# Model-based glycaemic control using subcutaneous insulin for in-patients

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# Abstract

Dysregulation of blood glucose (BG) levels can occur due to either the influence of stress hormones and external drugs in the critical care setting or a developed resistance/impairment to glucose regulation as seen in Type 1 and 2 diabetes. In both situations, external intervention to assist in regulating BG levels has shown reductions in morbidity and mortality. A method that has proven effective in the Intensive Care Unit (ICU) is the Stochastic TARgeted (STAR) model-based Glycemic Control (GC) protocol, which uses a combination of population-based stochastic models and Model Predictive Control (MPC) to provide safe and effective GC. Therefore, this type of GC may prove effective for out-patient type 2 diabetics. However, STAR is developed for the ICU setting and more specifically the model used, the Intensive Control Insulin Nutrition Glucose (ICING) model, is developed based on ICU patient characteristics and is not necessarily suitable for the out-patient setting.

This research attempts to develop the STAR protocol and associated ICING model for better suitability of out-patient GC. In-silico and clinical data sets are used to review and develop control methodologies and technologies, and their impact on GC and outcomes. In addition, a clinical trial is designed to better understand the metabolic behaviour of type 2 diabetes, and enable improved, safer control of this cohort.

The representation and use of the ICING model-based insulin sensitivity ($S_I$) is investigated and validated in the ICU setting. Linear interpolation of sparse BG measurements was proven to give the best estimate of intermediate BG dynamics (mean RMSE 0.39 mmol/L). Minutely resampling of the interpolated BG measurements is shown to give the best representation of GC performance characteristics when GC protocol's measurement frequency and sparsity varied. The stochastic model currently used by the STAR controller was shown to represent both the Christchurch, New Zealand (NZ) and Gyula, Hungary ICUs well, with the $S_I$ variability being within the controllers current stochastic model bounds consistently equal to or greater than 90% of the time. Piece-wise polynomial approximations of the stochastic models were shown to represent the currently used bounds well (All $R^2$ values $> 0.96$) and provide approximately equal GC performance (% time in

BG band 4.4-8.0 mmol/L, 87.9% vs. 87.5%, P=0.67) and safety (BG measurements $< 2.22$ mmol/L, 9 vs. 8 measurements, P=1.0) in virtual trials. Continuous 2nd order B-spline basis function (BF) were shown to provide a much more physiologically realistic representation of $S_I$, providing a more realistic fit of point of care (PoC) measurement error compared to the currently used stepwise constant BFs (fitting error variance, 2.4% current zeroth order B-spline BF and 6.0% 2nd order B-spline BF vs. 6.0% published glucometer error).

The STAR GC protocol's clinical data was reviewed and areas of improvement investigated. Clinical data from STAR in Christchurch Hospital ICU, NZ and Kálmán Pándy Hospital ICU, Gyula, Hungary since 2011 was reviewed in terms of GC performance and safety. STAR was shown to provide approximately equally effective GC performance (86.6% and 87.1% time BG 4.4-8.0 mmol/L, respectively) and safety (patients with BG $< 2.22$ mmol/L, 4/292 Christchurch, and 2/47 Gyula) in both cohorts. These results were confirmed by the high data entry compliance of information entered into the STAR tablets, with the lowest compliance being in the feed related interventions (86.5% enteral nutrition (EN), and 88.2% parenteral nutrition (PN) interventions). STAR was also shown to be able to provide higher or equivalent feed rates than the best unit surveyed in an international survey of 150 ICUs over 20 different countries, while still providing safe and effective GC. Stepped by day feeding protocols were shown to provide a promising alternative to the currently used variable feeding regime used by STAR, significantly reducing workload (19.8% reduction) while maintaining GC performance and safety. A new STAR framework was developed, Stochastic Model Predictive (STOMP) control, that evaluated interventions based on a series of cost functions with longer 6 hour prediction horizon, improving clinical flexibility and allowing for longer 4 hour measurement intervals. All of these outcomes serve to validate and the modelling and control methods for GC in less acute wards and eventually the out-patient setting.

The type 2 diabetic and pre-diabetic out-patient was investigated to develop our understanding of their metabolic characteristics. An clinical trial was designed assess the effects of exogenous basal insulin on endogenous insulin production of type 2 diabetic and pre-diabetic out-patients, and collect data related to their metabolic characteristics. The initial results of this trial are presented and the

trial logistics discussed. No major concerns of patient discomfort and safety arose from the initial 2 patients. These results are a first step towards addressing type 2 diabetes using model-based basal insulin support early in treatment.

Overall, the research performed in this thesis was designed to develop the STAR protocol and associated ICING model for GC of out-patients with pre-diabetes and type 2 diabetes. Linearly interpolation of sparse raw BG measurements allows for more accurate identification of model-based $S_I$ and minutely or hourly resampling provides a fairer assessment of GC protocol performance. The stochastic models used by STAR capture patient $S_I$ variability well, while being approximately generalizable across independent cohorts, and can be approximated with piece-wise polynomial functions for easier use. A considerably more physiologically realistic representation of the ICING model's $S_I$ was created, better representing BG measurements and the associated error. The developed representation of $S_I$ would more optimally interpolate sparse, variable data and could be easily applied to sparser out-patient data. The STAR GC protocol was simplified and made more clinically flexible, while maintaining GC performance and safety, through the introduction of piece-wise polynomial stochastic models, a minimal workload stepped feeding protocol, and cost function control methodology (STOMP). Ultimately, these analyses better validate and incrementally simplify STAR for the out-patient setting. Finally, a clinical trial was designed and implemented to investigate basal insulin therapy for out-patients with pre-diabetes or type 2 diabetes, and develop our understanding of this cohort's metabolic characteristics.

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# Chapter 1

# Introduction

Multiple organs and physiological processes are involved in the regulation of BG. Dysregulation of BG levels occur whenever there are irregularities in the function of any key metabolic regulatory organs and/or hormones. It has been shown, in a range of clinical settings, that this BG dysregulation is associated with increased morbidity and mortality.

These irregularities may be due to either the influence of stress hormones and external drugs in the critical care setting or a developed resistance/impairment to glucose regulation as seen in type 2 diabetes. In both situations, external intervention to assist in regulating BG levels has shown benefit. A method that has proven effective in the ICU is the STAR model-based GC protocol.

The ICU GC protocol STAR is unique in the respect that it is a tablet-based protocol which uses a combination of population based stochastic models and MPC to provide safe and effective GC. This type of GC has not been attempted before in the out-patient setting. STAR is developed for the ICU setting and more specifically, the model used, the ICING model, is based on ICU patient characteristics. Therefore, for the STAR GC protocol to be used in an out-patient setting the model and GC methodology needs to be adapted.

This research attempts to develop the STAR protocol and associated ICING model for better suitability of out-patient GC. In-silico and clinical data sets are used to review and develop control

methodologies and technologies, and their impact on GC and outcomes. In addition, a clinical trial is designed to better understand the metabolic behaviour of type 2 diabetes, and enable improved, and safer control of this cohort.

## 1.1 The Glucose Regulatory System

Energy for cellular function in the body is created by the food in which we consume. The majority of the cells within the body are able to source this energy from fats, proteins, and carbohydrates. However, the brain is only able to source energy from glucose (carbohydrates). Thus, the accessibility of glucose is critical to brain functionality. This section discusses the how the body processes and regulates glucose, and the reasons why BG levels are strictly regulated.

### 1.1.1 Metabolic Energy

The majority of functions performed by a cell require energy (free energy) to create a chemical equilibrium shift and favour a forward reaction. A cell generates free energy by hydrolysing Adenosine Tri-phosphate (ATP), stores of free energy [1]. The body can source ATP from either fats, proteins or carbohydrates. However, the Central Nervous System (CNS) requires the majority of its energy to come from glucose (Carbohydrates) [2]–[4] as protein and fat oxidisation into ATP is not as efficient [5]. ATP created from carbohydrates is commonly created by the oxidation of glucose in the cytosol of a cell (Glycolysis), where each molecule of glucose creates 36 molecules of ATP [1], [5].

Carbohydrates commonly found in food can be either simple sugars (monosaccharides), such as glucose, fructose, and galactose, double sugars (disaccharides), such as sucrose, lactose, and maltose or sugar stores (polysaccharides), such as glycogen and starch. However, all disaccharides and polysaccharides are eventually broken down into monosaccharides before being used to create energy [1]. As carbohydrates make up approximately 45% to 65% of a typical individuals diet [4], [6], they provide the most common source of glucose used by a cell in the generation of ATP.

### 1.1.2 Glucose Transportation

Carbohydrates consumed by a person are typically absorbed through the small intestine. Monosaccharides can be absorbed directly, whereas polysaccharides need to be broken down by the mouth and stomach digestive enzymes, and disaccharides are broken down by enzymes on the luminal wall of the small intestine [7]. Once absorbed through the small intestine, monosaccharides then enter the blood stream to be distributed throughout the body and capillary beds for cellular energy usage and storage in the CNS, liver (glycogen stores), muscles, adipose tissue and kidneys [8]–[11].

Glucose diffuses into the interstitial fluid through small spaces between endothelial cells, lining the capillary beds, with changes in hydrostatic and osmotic pressure [12]–[14]. However, in the brain the endothelial cells are joined by tight junctions and thus glucose is unable to easily diffuse through (Blood brain barrier), and are instead actively moved by transport proteins (GLUT-1) inside the endothelial cells, into the brain interstitial fluid [15], [16]. Once glucose is within an interstitial fluid, it is actively transported into cells by the means of 1 of 4 different glucose transport proteins, GLUT 1-4 [17], [18].

### 1.1.3 Glucose Regulation

As the availability of glucose in the blood is critical to brain and body functionality, complications occur if the BG levels are too low (Hypoglycaemia) [19]–[21] or too high (Hyperglycaemia) [22]–[24]. Hypoglycaemia is associated with increased risk of micro- and macro- vascular events, coronary events [25], [26], and mortality [27], [28] in individuals with diabetes, and increased morbidity [29], length of stay [30], organ dysfunction [30], [31], and mortality [29], [30], [32]–[36] in critically ill individuals. In addition, hyperglycaemia or very high BG levels are associated with increased morbidity [37]–[39], and mortality [40] in individuals with diabetes, and increased morbidity [29], [41]–[47], length of stay [44], [46], and mortality [41]–[45], [47]–[51] in critically ill individuals.

If hyperglycaemia occurs, the body's natural response is the release of insulin, a peptide hormone secreted by the Islets of Langerhans within the Beta cells of the pancreas [52]. Insulin binds to a surface receptor of a cell, signalling a complex cascade of inter-cellular events, activating the

GLUT4 transport protein to move to the plasma membrane and facilitating glucose uptake [53]. Insulin activates glucose uptake in adipose tissue, the liver (hepatic tissue), and muscle cells and its conversion into glycogen stores (glycogenesis) [17], [18]. In addition, the release of insulin suppresses the endogenous production of glucose by the liver and/or, to a lesser extent, the kidneys [54], [55].

The body's natural response to hypoglycaemia is the production and release of glucose into the blood stream. This endogenous glucose production is facilitated in 2 ways, by gluconeogenesis and/or glycogenolysis. Gluconeogenesis is the creation of glucose from non-glucose substrates, predominantly lactate, glutamine and alanine, and glycogenolysis is the breakdown of glycogen stores into glucose [56]. Gluconeogenesis occurs in both the liver and the kidneys, and is triggered by the release of hormones, such as adrenaline, by the brain [9]. Whereas, glycogenolysis has only been seen to occur in the liver and is triggered by the release of glucagon by the pancreas [57], [58].

There is currently much debate over the body's *'natural'* BG level, and it is likely patient-specific [59]. From birth, BG has been seen to be naturally regulated between 3.5-5.5 mmol/L [59]. However, this level tends to increase with age [60]. In addition, regulating BG between 4.4 and 8.0 mmol/L has shown associated benefits for non-diabetes ICU patients [61]–[63]. These results imply healthy individuals have a *'natural'* BG level around these reported ranges. In contrast, an individual with diabetes can have a higher *'normal'* BG level specific to the glycaemic thresholds they have developed over time and exposure [59], [62], [64], although a lower glycated haemoglobin ($HbA_{1c}$) of 7% (approximately 8.3 mmol/L BG average [65]) results in improved outcomes for individuals with diabetes [66]. A summary diagram of the body's natural BG regulation process can be seen in Fig. 1.1.

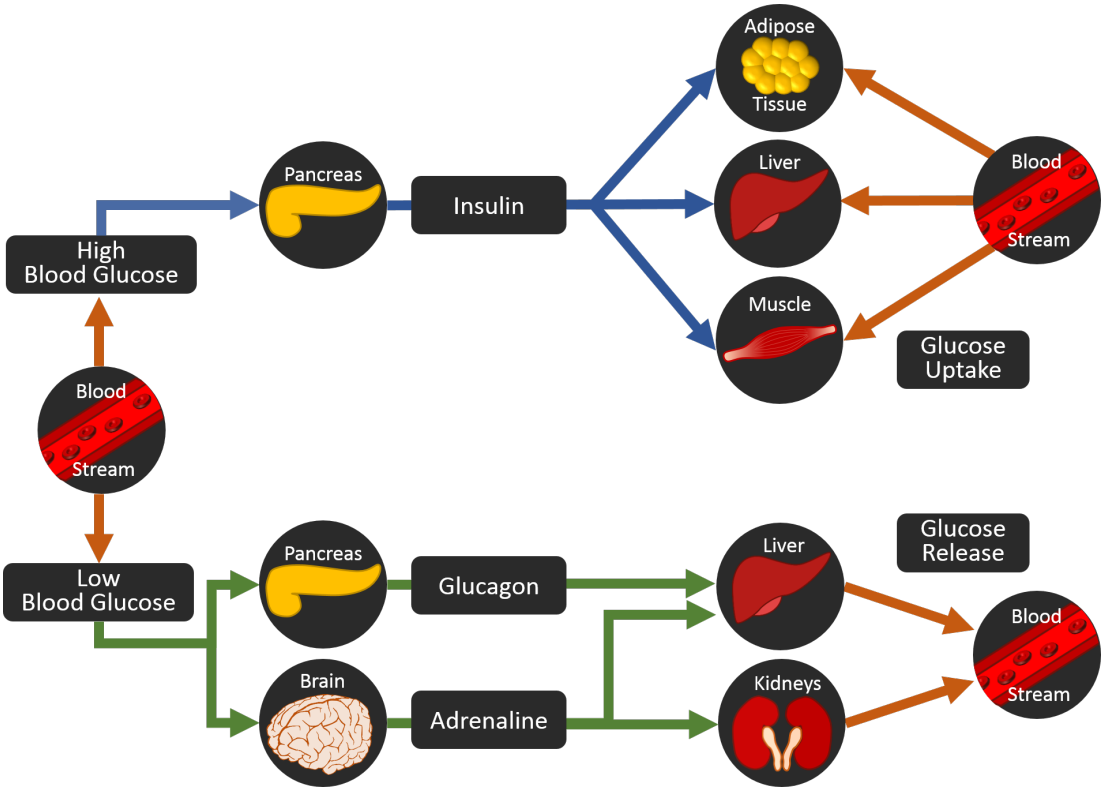



Figure 1.1: Summary of blood glucose regulation processes.

The ability for insulin to bind to cellular receptors and the presence of the many important signalling molecules involved in activating the GLUT4 transport protein significantly contributes to an individual's SI $S_I$, also known as insulin resistance [53], [67], [68]. An individual's overall $S_I$ is determined by the ability to uptake glucose, given an amount of insulin. The current gold standard measure of $S_I$ is the hyper-insulinemic, euglycaemic clamp test [69]. However, various other simpler model-based tests have been developed to approximate $S_I$ [70]–[72].

## 1.2 Glycaemic Control in the Intensive Care Unit

In the ICU a patient's body is under considerable stress as it attempts to recover from severe injury and/or infection. The body's stress response during this period can be broken up into 2 key stages, the *ebb* and *flow* phase [73]. Each stage results in a variation of hormones present, and metabolic responses. This section discusses how glucose regulation is effected by this stress response and clinical treatment in an ICU patient's recovery, and how external intervention can be used to assist in BG regulation.

### 1.2.1 Hyperglycaemia in the Critical Care

The *ebb* phase typically lasts around 12-24 hours after injury [73], during which a large release of noradrenaline, adrenaline, and cortisol [74]–[77] causes significant changes in metabolic responses [39], [74], [77], [78]. High levels of these stress hormones stimulate hepatic and muscle glycogenolysis, and hepatic gluconeogenesis [79]–[81]. They also depress glycogenesis [82], [83] and inhibit insulin secretion [74], [84]. The combined effects result in 'stress-induced' hyperglycaemia [39], [85]–[88].

The *flow* phase occurs immediately after the *ebb* phase, and typically peaks around 3-5 days post-injury, subsiding by 7-10 days [39], [89]. During this period metabolism and catabolism is increased, resulting in increased glucose turnover and gluconeogenesis unresponsive to hyperglycaemia [90], [91]. In addition, the cortisol levels, a stress hormone, can remain relatively high during this phase [39], [92], [93].

In addition to body's the stress response, factors such as undiagnosed diabetes [94], commonly used metabolism modifying drugs [39], [95]–[97], and excessive feeding of high glucose content nutrition [98]–[100] can also increase the prevalence of hyperglycaemia in the ICU. There is also a significant amount of inter- and intra- patient variability in the influence of these factors. As a result, 'stress-induced' hyperglycaemia is commonplace in the ICU [41], [51], [86].

### 1.2.2 Glycaemic Control Benefits and Limitations

The observed relationship between hyperglycaemia morbidity and mortality outcomes in the ICU [29], [41]–[51] has led to GC protocols being regularly employed in the ICU. Studies have shown that safe, effective GC that modulates exogenous insulin and/or nutrition, significantly reduces mortality and morbidity [29], [30], [51], [101], [102], organ failure [31] and cost of care [103], [104]. However, due to the variability in a patient's response [103], [105]–[111], some GC protocols have failed to provide consistently safe and effective outcomes, resulting in an uncertainty of the benefits of GC [103], [109], [112]–[117].

Two common characteristics of ineffective GC protocols are hypoglycaemia and glucose variability. Both outcomes are independently associated with increased mortality [34]–[36], [118]–[120]. This failure of GC is usually a result of the GC protocol's inability to handle the highly complex, variable and dynamic stress response of an ICU patient. Specifically, the intra- and inter- patient variability [121]–[125]. These variabilities are the fundamental reason why safe, effective GC is difficult.

### 1.2.3 Glycaemic Control Protocols

ICU GC protocols are commonly in the form of either a flowchart or model-based prediction software (MPC), which recommend insulin treatments to clinical staff. The simplest example of a flowchart GC protocol is the sliding scale protocol in [29], which recommends an insulin dose based on difference between the patients current BG and target BG level. Since this early sliding scale, many more complex flowchart algorithms have been developed, which also consider factors, such as the of rate of change of BG and previous interventions given [101], [109], [126], [127].

In contrast, MPC GC protocols use a physiological model and clinical measurements to define patient specific metabolic behaviour. This information is then used to choose the intervention resulting in the optimum future BG [128]–[130]. In addition, some GC protocols also modify the amount of exogenous nutrition given to a patient in addition to the insulin dose administered [101], [128]. However, the implications of this added control input are still unknown and it is currently heavily debated as to whether lowering an ICU patient's caloric intake is beneficial [131]–[136].

For a GC protocol to be effective in the ICU it needs to:

1. Effectively lower or eliminate mild and moderate hyperglycaemia (BG $>$ 8.0 mmol/L, BG $>$ 10.0 mmol/L).
2. Have a low occurrence of mild and severe hypoglycaemia (BG $<$ 4.0 mmol/L, BG $<$ 2.2 mmol/L) [137].
3. Have a low workload and compliant protocol [137]–[141]. Often assessed by BG measurement rates.

A GC protocol which best meets these characteristics should provide the best time in the intermediate BG band of 4.0-8.0 mmol/L and have the best chance of improved patient outcomes [61], [142], [143], as seen previously in [29]. These characteristics are compared for 7 different GC protocols in Table 1.1. As the statistics reported in literature are inconsistent, Table 1.1, direct comparison of the GC protocols is difficult. However, as the distribution of BG is typically log-normal [144]–[146] an estimate of the GC protocol's CDF can be made by fitting a log-normal distribution to the statistics published. The estimated log-normal CDF of BG for each protocol can be seen in Fig. 1.2.

Note these fitted log-normal CDF's only approximate study performance and can vary due to a small changes in the reported statistics. In addition, the results reported for the LOGIC-1 protocol [130] were intention to treat, and thus are positively biased when directly compared to only treated patients in other GC protocols. Moreover, only the mean and standard deviation was able to be used for fitting from the very limited statistics presented in the NICE-SUGAR study and appendices[126].

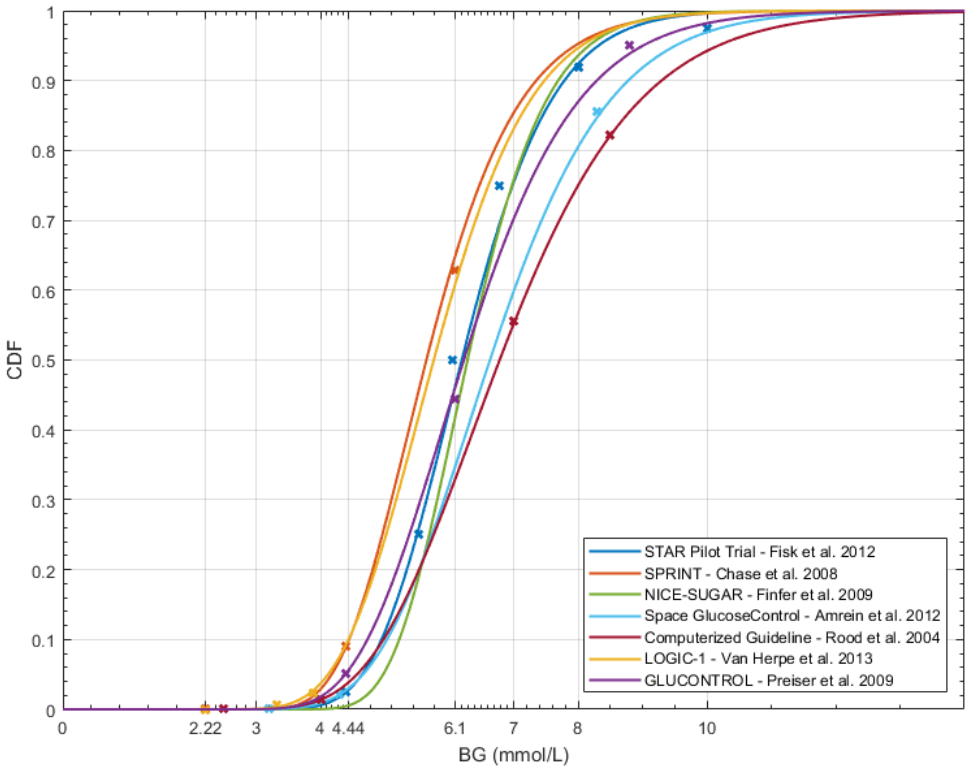



Figure 1.2: Comparison of the estimated log-normal CDF for each GC protocol based on the respective statistics reported in literature.

Table 1.1: Comparison of 7 different Glycemic Control (GC) protocols found in literature in terms of performance, safety and workload using the respective statistics published.

| Protocol | STAR [128] | LOGIC [130] | SGC (eMPC) [129] | SPRINT [101] | NICE-SUGAR [126] | GLUCONTROL [109] | Comp. Guideline [127] |
|---|---|---|---|---|---|---|---|
| Type | MPC | MPC | MPC | Flowchart | Flowchart | Flowchart | Flowchart |
| # Patients | 10 | 149 | 20 | 371 | 3016 | 536 | 66 |
| Per-patient Performance | | | | | | | |
| BG Mean (mmol/L) | 6 | 5.9 | 6.8 | 6 | 6.39 | 6.5 | 6.5 |
| BG SD (mmol/L) | 0.93 | 0.5 | 0.4 | 1.3 | 1 | 2 | 1.2 |
| % Time >10 | 2.48 | - | - | - | - | - | - |
| % TIB 4.4-8.0 | 89.4 | - | 83.4 | - | - | - | - |
| % TIB 4.4-6.1 | - | 68.6 | - | 53.9 | - | 39.3 | - |
| % Time <4.4 | 2.48 | - | 2.13 | 9 | - | 5.1 | - |
| % Time <2.2 | 0 | - | 0 | 0.1 | - | 2.4 | - |
| Safety | | | | | | | |
| % Patients <3.9 | - | 32.2% | - | - | 87.1% | - | - |
| % Patients <3.3 | - | 14.1% | 20.0% | - | - | - | - |
| % Patients <2.2 | 0.0% | 0.0% | - | 5.2% | 6.8% | 8.7% | 0.0% |
| Workload | | | | | | | |
| Meas. Int. (Hours) | 1.8 (-) | 2.2 (0.4) | 2.0 (0.4) | 1.6 (0.3) | - | - | - |

*Model Predictive Control (MPC) blood glucose (BG), standard deviation (SD), time in band (TIB). Data presented in Mean (standard deviation (SD)) where appropriate.

As seen in Fig. 1.2 and Table 1.1, in general, MPC is more effective and safer GC compared to flowchart based GC protocols, spending more time in the targeted region while reducing the occurrence of hypoglycaemia. The rates of hypoglycaemia (BG $<$ 2.22 mmol/L) reported by SPRINT, NICE-SUGAR and GLUCONTROL although low, are relatively high compared to the other GC protocols. In addition, the estimated percentage of hyperglycaemia (BG $>$ 10.0 mmol/L) from Fig. 1.2 is relatively high for both the Space GlucoseControl and Computerized Guideline, showing that they are not as effective in lowering a patients BG compared to the other GC protocols. As mentioned earlier, the results presented in LOGIC-1 were based on the intention to treat [130], therefore the reported statistics and estimated BG distribution could be heavily biased by "stable" patients with normal glycaemia. Thus, STAR provides the most promising ICU GC protocol of the protocols reviewed. However, deeper investigation into the STAR GC performance is required before improvements can be made. In addition, the very low number of patients (N = 10) on the STAR protocol limit the validity of the results presented.

### 1.2.4 Stochastic Targeted (STAR) Glycaemic Control

The tablet-computer-based STAR GC protocol provides patient-specific GC [128], [147] by using a clinically evaluated pharmaco-kinetic and pharmaco-dynamic model of the insulin-glucose system (ICING) [31], [148] and a cohort based model of $S_I$ variability [145], [149] to compute optimal insulin and nutrition interventions. STAR aims to maximise time in the targeted band (4.4-8.0 mmol/L) and nutrition, while maintaining a maximum 5% risk of BG $<$ 4.4 mmol/L [128], [147]. STAR offers 1-3 hourly BG measurement frequencies to allow nurses to manage workload [150], [151]. STAR has been the standard of care in Christchurch Hospital ICU, Christchurch, New Zealand and in the Kálmán Pándy Hospital ICU, Gyula, Hungary since 2011. Note the predecessor of STAR in Christchurch was the paper-based, model-derived [152], SPRINT GC protocol [31], [101].

Starting criteria for STAR is two successive BG measurements over 8.0 mmol/L within a 4-h period. After 2 measurements are taken, integral based parameter fitting [153] is used to identify a model-based $S_I$, Eq. (1.1) [31], [148], [154]. This value is used with a stochastic model, based on historical data [128], [145], [149], [155], to find the $5^{th}$ and $95^{th}$ percentile potential future $S_I$ values.

These $5^{th}$ and $95^{th}$ percentile $S_I$ values and a potential insulin and nutrition intervention are then used to forward-simulate the likely resulting $5^{th}$ and $95^{th}$ percentile BG values for that intervention. This process is iterated over many possible interventions to find the intervention with 5% risk of BG $<$ 4.4-4.6 mmol/L and the maximum likely time in the targeted 4.4-8.0 mmol/L band [128], [147].

STAR modifies nutrition rate depending on the bounds of predicted potential behaviour, with a preference to increase insulin before reducing nutrition, and to raise nutrition whenever possible [128], [147]. STAR modulates this nutrition rate between 30-100% of the caloric goal, with a maximum step change of $\pm$30% caloric goal per hour [128]. American College of Chest Physicians (ACCP) guidelines are used to determine patient-specific daily caloric goal intake of 25 kcal/kg/day [156].

STAR is a risk-based MPC GC protocol. It is the only GC protocol to use an estimated future variability, and thus risk, in dosing. It thus doses to an outcome BG range, rather than an outcome target BG level.

The ability for the ICING model to capture metabolic physiology directly determines the physiological representation, and inter- and intra- patient variability of $S_I$. Prior iterations of the ICING model-based $S_I$ were shown to correlate well with clamp measurements [72], [157]. However, as the physiological model has developed, the modelled representation of $S_I$ and it's variability will have changed and consequently influenced the GC performance of the STAR protocol. Therefore, improving the modelled representation of $S_I$ is the best route to improving GC performance, and safety.

#### *1.2.4.1 ICING Model*

The current model used by STAR is a variant of the Intensive Control Insulin Nutrition Glucose (ICING) model [148], [158], defined:

$$\dot{G}(t) = -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \tag{1.1}$$

$$\dot{Q}(t) = n_I(I(t) - Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \tag{1.2}$$

$$\dot{I}(t) = -n_K I(t) - n_L\frac{I(t)}{1+\alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + (1-x_L)\frac{u_{en}(G)}{V_I} \tag{1.3}$$

$$P(t) = min(d_2 P_2, P_max) + PN(t) \tag{1.4}$$

$$\dot{P_1}(t) = -d_1 P_1 + EN(t) \tag{1.5}$$

$$\dot{P_2}(t) = -min(d_2 P_2, P_max) + d_1 P_1 \tag{1.6}$$

$$u_{en}(G) = min(max(u_{min}, k_1 G(t) + k_2), u_{max}) \tag{1.7}$$

Where the key variables are described in Table 1.2, and the remaining model parameters, rates and constants are described in [122], [148].

Table 1.2: Key variables of the ICING model.

| Variable | Unit | Description |
|---|---|---|
| $G(t)$ | mmol/L | Blood glucose concentration |
| $I(t)$ | mU/L | Plasma insulin concentration |
| $Q(t)$ | mU/L | Interstitial insulin concentration |
| $P(t)$ | mmol/min | Glucose appearance in plasma from dextrose intake |
| $S_I(t)$ | L/(mU.min) | Insulin sensitivity |

#### *1.2.4.2 Insulin Sensitivity ($S_I$)*

For an out-patient, under steady state conditions, $S_I$ is considered to be relatively constant. Due to an ICU patient's hormonal stress response and/or the drugs given, $S_I$ can fluctuate significantly over short periods of time [31], [112], [122], [145]. Therefore, a dynamic interpretation of $S_I$ is required to model a patient's behaviour in the ICU.

A key characteristic of the STAR GC protocol, and main contributor to its performance, is its ability to capture inter- and intra- patient variability through hour to hour changes in a patient's $S_I$. However, as $S_I$ is fitted hourly, step-wise, to historical data it may also erratically change to best fit the historical BG data, capturing BG, as well as any non-modelled dynamics. Therefore, again, an improvement in the ICING model could reduce erratic, non-physiological $S_I$ fluctuations, narrow the bands of the stochastic model, and, ultimately, improve the GC performance and safety of STAR.

## 1.3 Glycaemic Control in Out-patients with type 2 Diabetes

The prevalence of diabetes mellitus in the world has dramatically increased over the past decade. In NZ alone, prevalence has increased from 3.8% to 5.5% (approximately 193,000 People) [159], with approximately 800 people dying from it each year (92% having type 2 diabetes) [159], [160]. This section discusses diabetes and how type 2 diabetes is currently managed in NZ.

### 1.3.1 Type 1 and 2 Diabetes

Type 1 diabetes, is commonly the result of autoimmune destruction of the insulin producing cells in the pancreas (Beta cells in Islets of Langerhans) as a result of a genetic or other disorder [161]. The rate of destruction of Beta cells varies between individuals, but ultimately results in little-to no endogenous insulin production [162]. This loss results in the need for exogenous insulin administration to mimic normal insulin secretion behaviour and lower BG levels.

In contrast, type 2 diabetes is more commonly the result of poor health, sedentary lifestyles, and diet, leading to both insulin resistance and deficient insulin secretion. Consequently, BG levels are not able to be lowered to euglycaemia via normal physiological mechanisms [162]. As type 2 diabetes is a progressive condition, treatment depends on an individual's specific progression. This issue complicates treatment of type 2 diabetes due to the unknown and variable ability someone with type 2 diabetes has to control their own BG levels with normal physiology, before requiring insulin or other drugs.

Prolonged hyperglycaemia, resulting from untreated diabetes can lead to blindness (Retinopathy), amputation (Neuropathy), cardiovascular disease, stroke and renal disease [163]–[167]. Moreover, it has been shown that a significant reduction in a diabetic individual's morbidity and mortality can be achieved if euglycaemia can be maintained [165], [168]. However, because this level of control has proven very difficult, the tangible costs of type 2 diabetes alone in NZ are estimated to be over $1.3 billion and to rise to $1.7 billion by 2021 [169], [170], approximately 0.5% of GDP [171] and approximately 10% of the total health care budget [172]. This cost is unsustainable and must be reduced.

Currently in NZ, diagnosis of type 2 diabetes is based on an $HbA_{1c} \geq 6.7\%$ (50 mmol/mol) or a fasting BG $\geq 7.0$ mmol/L or one BG measurement $\geq 11.1$ mmol/L [173]. An $HbA_{1c}$ measurement provides a weighted measure of the mean BG over the previous 120 days [174]. However, as these tests are only typically performed when there is a suspicion of diabetes, it is estimated that approximately 25% of people with diabetes are undiagnosed [175]. It has been shown if type 2 diabetes is treated early and *'effectively'*, its progression can be stopped and normo-glycaemia maintained [176]–[178], reducing the associated long term health care costs. However, if not treated effectively their condition completely degrades, secreting only negligible amounts of endogenous insulin. At this point their condition becomes very similar to an individual with type 1 diabetes in terms of treatment [179]–[181]. However, such treatment is difficult, costly and often not robust. Hence, as the progression of type 2 diabetes can be slowed or stopped, preventative treatment is the focus of this research. A simplified summary of the progression of type 2 diabetes, based on similar figures in [176], [178], [182]–[185], can be seen in Fig. 1.3. The goal of this research is to intervene as early as possible in this figure at the beginning of impaired glucose tolerance (IGT), rather than later in the type 2 diabetes region.

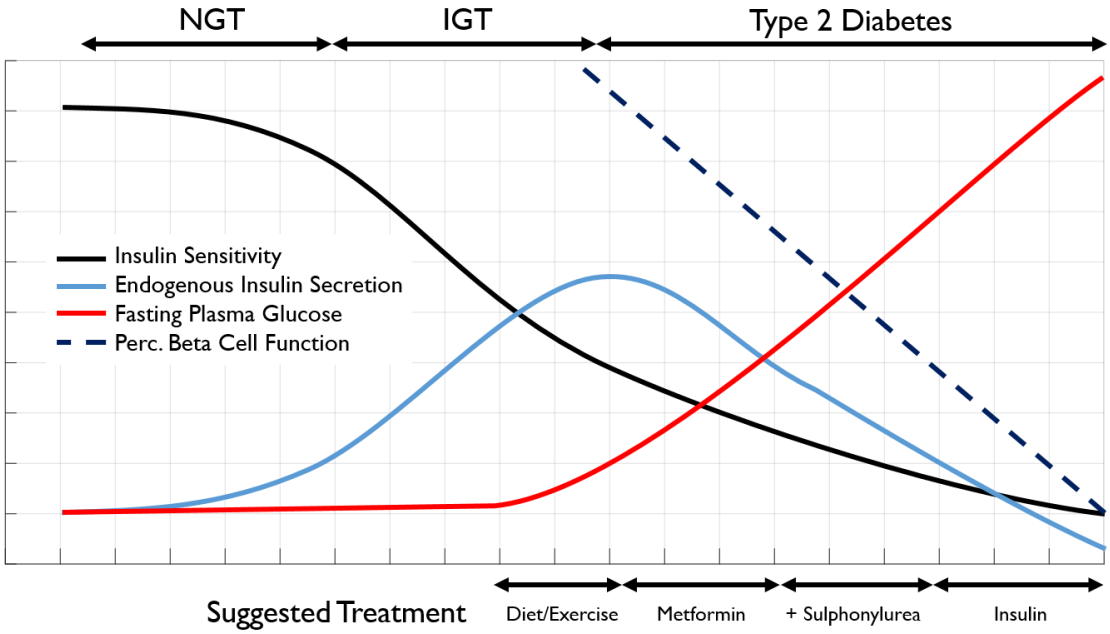



Figure 1.3: Simplification of the changes in glucose regulatory factors throughout the progression of type 2 diabetes, including normal glucose tolerance (NGT) and impaired glucose tolerance (IGT), and its current relationship to the treatments offered based on data published in [176], [178], [182]–[184]

### 1.3.2 Current type 2 Diabetes Treatment

After the initial diagnosis of type 2 diabetes, the first treatment option suggested is generally a significant change in lifestyle (Diet and exercise) to try and lower the individual's $HbA_{1c}$ [162], [181]. If the targeted HbA1c is not met after 3 months assistive oral medication is recommended. Currently in NZ, the initial recommended medication for type 2 diabetes is Metformin (Apotex NZ Ltd., New Zealand) [186]. Metformin acts by increasing the biological efficiency of available insulin, increasing glucose uptake and effectively increasing a patient's sensitivity to insulin [181], [187] and has been proven effective in improving patient outcomes [188]. If the individual's condition still deteriorates they are prescribed Sulphonylurea [186], which acts as a steroid to increase pancreatic insulin output (endogenous insulin secretion) [181], [189]. However, it has been shown that 9 years after the prescription of sulphonylurea, approximately 80% of patients will still require insulin treatment [25], [190], where insulin is the last available treatment option [183], [186], [191]. The approximate timing of suggested treatments in relation to the progression of diabetes can be seen in Fig. 1.3.

Insulin therapy for type 2 diabetes usually begins with basal insulin support [179]–[181], where basal insulin is a subcutaneous long acting analogue of insulin which is designed to be released slowly and steadily into the blood stream over a long period of time (Typically 16+ hours). The most common commercially available forms of long acting insulin are Glargine and Detemir. Basal insulin support is designed to mimic the normal basal insulin production of the pancreas [179]–[181], [183], leaving the pancreas free to act around meals. The most common dosing regime is a sliding scale proportional to the individual's morning fasted BG week long average [180], [192], [193]. However, if an individual's condition deteriorates even further they are prescribed both basal and rapid acting insulin to try and mimic the entire functionality of the pancreas [179]–[181], [183], similar to type 1 diabetes treatment [183], [194].

### 1.3.3 Basal Insulin Therapy

Many studies have discussed and compared the treatment options for type 2 diabetes, specifically with regard to GC and beta cell degradation (endogenous insulin secretion). It has been shown in many cases that insulin treatment is more effective in preserving beta cells [25], [168], [195], [196], improving lipid metabolism [197]–[200], and achieving GC targets [25], [164], [190], [201] compared to other offered treatments. This result may be due to those receiving oral medication still requiring relatively high endogenous insulin secretion rates from the pancreas, leading to the eventual *'fatigue'* of the pancreas [161], [202]–[205]. Therefore, treating type 2 diabetes with basal insulin, much earlier, may allow the pancreas to *'rest'*, reducing endogenous insulin secretion [206], [207], in between meals and thus allowing it to act more appropriately during meals [208]. Ultimately, this approach suggests basal insulin therapy may improve GC and reduce the degradation of an individual's pancreatic functionality.

However, basal insulin therapy is usually only offered after an individual with type 2 diabetes condition has substantially progressed, and beta cell endogenous insulin production is likely significantly depleted Fig. 1.3 [176]. This is largely due to the perceived risks associated with insulin therapy [64], [66], [164], [180], [201], [209]–[211]. Therefore, starting basal insulin therapy this late in the progression of type 2 diabetes may not allow the potential benefits of insulin therapy to be best utilised. One study in particular looked at prescribing people age 50 and over, with evidence of cardiovascular disease and newly detected or established diabetes (pre-diabetes or early stage type 2 diabetes), with standard practice diabetes treatment or one daily injection of Glargine (Basal insulin) for 6 years [212]. The primary outcomes were in regard to cardiovascular events, and no conclusive outcome was found. However, a 41% reduction in the number of people with newly diagnosed diabetes was seen in the group which used basal insulin therapy compared to those who were receiving standard treatment [193], despite having significant numbers who quit this therapy or were not fully compliant. This outcome strongly emphasises the potential benefits of early basal insulin therapy, which is otherwise not used clinically.

Although basal insulin therapy may have potential benefits, it increases the risk of hypoglycaemia

if not taken correctly [64], [66], [164], [180], [201], [209]–[211]. It thus is avoided clinically for this reason [191], [201]. In addition, there is also a negative stigma around starting insulin therapy, as individuals and the physician feel they have failed [183]. Therefore, before early basal insulin therapy can be offered, a very safe and effective dosing protocol needs to be developed. Only then can the potential benefits of early basal insulin therapy be realized.

As seen by the GC offered in the ICU (Section 1.2.3) one of the best ways to ensure a safe dosing regime, is by using a MPC GC protocol, preferably in this case, a risk-based protocol. To allow a MPC GC protocol to be formed, an effective model needs to be developed which includes subcutaneous insulin action and any other added relevant dynamics. Facilitating the prediction of glucose trends in type 2 diabetes and the expected endogenous insulin response to exogenous insulin are particularly important needs, not already available for this model or any other.

## 1.4 Summary

Glucose is found in carbohydrates and is essential to body and brain functionality as it is the most common and efficient source of ATP energy for cellular function. Thus, the body naturally regulates BG with the pancreas, liver, and kidneys to a likely patient-specific BG level. If an individual's BG level is too low or high (hypo- and hyper- glycaemia, respectively) complications arise, which have been shown to be associated with increased morbidity and mortality in both diabetes and critically illness. Hyperglycaemia is common place in the ICU, and significant benefits have been shown if BG levels are controlled to 'normal' levels. Model-based GC techniques have been shown to provide effective GC, with the STAR framework performing particularly well. However, a more comprehensive review of the STAR GC is first required to understand the strengths and weaknesses of the GC protocol. In addition, improvements in the physiological resemblance of the ICING model's interpretation of $S_I$ could improve STAR's GC and applicability to ward and out-patient GC. Therefore, the first part of this research is focused on reviewing and developing the STAR GC protocol, and updating the modelled representation of $S_I$ with the future expectation of providing GC to the wards and out-patients.

Finally, it is commonplace for an individual with type 2 diabetes condition to degrade on oral medication and insulin treatment is typically only offered after significant damage to the pancreas has occurred. This choice is made almost exclusively due to the risks of hypoglycaemia associated with insulin therapy. However, potential benefits may exist if insulin is used as an initial treatment option for GC. Therefore, the second part of this research is focused on gathering the required information to be able to safely use basal insulin therapy as the initial treatment option for type 2 diabetes in the wards.

# Part I:

# Improving the validity and representation of Insulin Sensitivity

If we knew what we were doing, it wouldn't be called research, would it?

Albert Einstein

# Chapter 2

# Interpretation of Retrospective BG Measurements

## 2.1 Background

ICU GC protocols use a range of different BG measurement intervals (0.5 – 4 hours), which may vary during treatment depending on a patient's condition [101], [109], [129], [213]–[215]. In particular, most GC protocols measure more frequently when out of their targeted band and less frequently when patients are *'stable'* [101], [109], [129], [213]–[215]. Therefore, the BG information recorded by each GC protocol has varying degrees of sparsity, with raw BG measurements commonly being more dense in areas of poor control. This variability and skewness of the raw BG measurements make fair assessment and comparison of GC protocol performance difficult, particularly when one key GC performance criteria is percentage of time within, above, and below the targeted BG range [137]. A common method to improve assessment fairness is to interpolate between BG measurements and sample the interpolated trace [101], [129], [214], [215]. However, the best interpolation technique and sample rate is still unknown.

[1] **K. Stewart**, F. Thomas, C. Pretty, G. Chase, and G. M. Shaw, "How Should We Interpret Retrospective Blood Glucose Measurements? Sampling and Interpolation," in 20th World Congress of the International Federation of Automatic Control, 2017.

Similarly, many insulin-glucose models use parameter identification techniques that require a similar approximation of the continuous BG dynamics [112], [216]–[221], which can significantly skew model fit and 'accuracy'. Many models and identification methods use linear interpolation between BG measurements as a first approach [148], [219]. However, the accuracy of linear interpolation in comparison to other interpolation techniques has not been assessed.

This chapter investigates the accuracy of 5 different BG interpolation methods over clinically typical 2, 3 and 4 hour measurement intervals. The effect of various sampling rates on the interpolated BG trace is also assessed in relation to the outcome of key GC performance statistics.

## 2.2 Methods

### 2.2.1 Patient Data

Patient data from patients treated with SPRINT and STAR in Christchurch Hospital ICU, NZ between 2005-2016 is used [101], [147], [215]. The Upper South Regional Ethics Committee, NZ granted approval for the retrospective audit, analysis and publication of the Christchurch Hospital patient data.

SPRINT is a paper based GC protocol which offers 1-2 hour measurement intervals and allows the time of BG measurements to be recorded to an hourly resolution [101]. In contrast, STAR is a tablet-based GC protocol which offers 1-3 hours measurement intervals and allows the time of BG measurements to be recorded to a resolution in minutes [147], [215]. To assess which interpolation technique best captures the intermediate BG dynamics a representative sample of the densely measured SPRINT cohort data is used [101]. The effect of sampling rate on GC performance statistics is assessed using the more sparsely measured STAR cohort data.

### 2.2.2 Interpolation techniques

Five interpolation techniques are investigated, separated into 2 types of interpolation:

1. *Piece-wise interpolation*: The interpolated trace goes through all of the measurement points.
2. *Fitted interpolation*: The interpolated trace is a combination of BF, best fit to the measured data points, as a whole, but can miss any individual point.

#### *2.2.2.1 Piece-wise interpolation*

Three Piece-wise interpolation techniques are investigated; linear, spline and cubic interpolation.

*Linear interpolation*: Data between BG measurements is assumed to be a linear line. Thus, continuous BG data is represented by a piece-wise 1st order polynomial.

*Spline interpolation*: Data between BG measurements is assumed to follow a spline using not-a-knot end conditions, continuous in both 1st and 2nd derivative. Thus, continuous BG data is represented by cubic interpolation of the spline.

*Cubic interpolation*: Data between BG measurements is assumed to be a cubic relationship, continuous in only the 1st derivative. Thus, continuous BG data is represented by a piece-wise cubic polynomial.

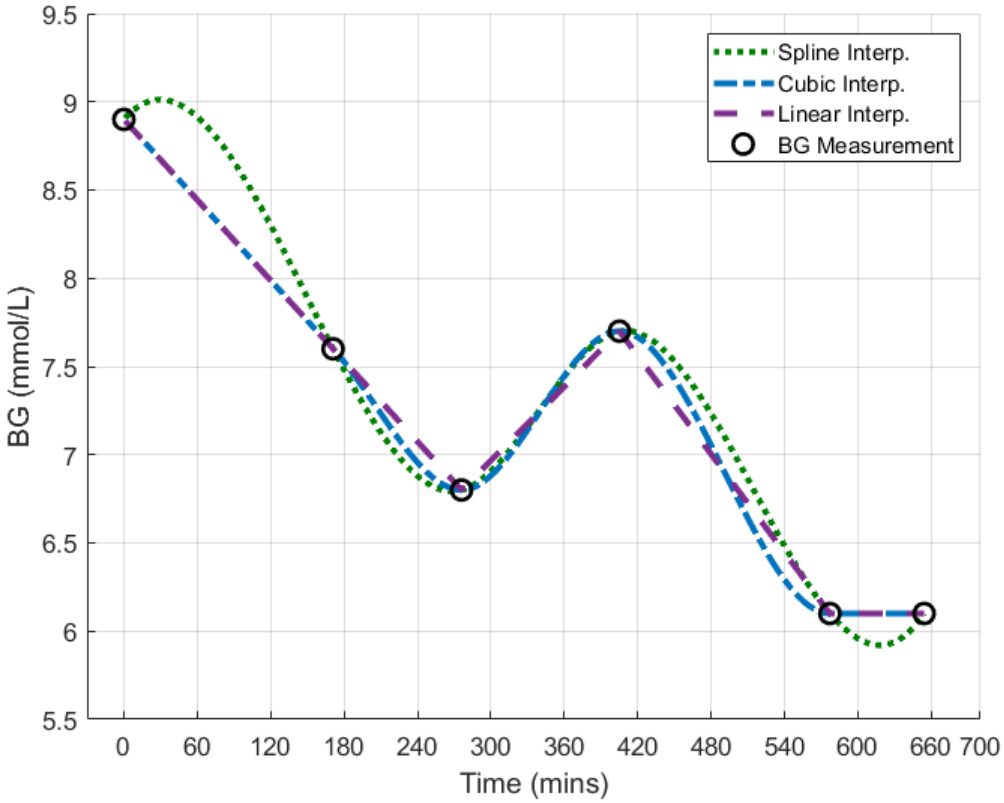



Figure 2.1: Example of the Piece-wise interpolation techniques being investigated.

*2.2.2.2 Fitted interpolation*

Two fitted interpolation techniques are investigated, each using 1st and 2nd Order B-spline BF fitting. Fitted interpolation is used to incorporate an approximation of the measurement error, and restrict over fitting rapid changes in the interpolated BG trace due to measurement error and outliers. BF widths were varied to investigate the best fit with this criteria. The interpolated BG trace, $G(t)$, is identified as the linear combination of BFs, $\Phi_n(t)$, minimizing the error between the identified and clinically measured BG:

$$\begin{bmatrix} \Phi_1(t_1) & \Phi_2(t_1) & \cdots & \Phi_n(t_1) \\ \Phi_1(t_2) & \Phi_2(t_2) & \cdots & \Phi_n(t_2) \\ \vdots & \vdots & \ddots & \vdots \\ \Phi_1(t_m) & \Phi_2(t_m) & \cdots & \Phi_n(t_m) \end{bmatrix} \begin{bmatrix} \gamma_1 \\ \gamma_2 \\ \vdots \\ \gamma_n \end{bmatrix} = \begin{bmatrix} BG_{meas}(t_1) \\ BG_{meas}(t_2) \\ \vdots \\ BG_{meas}(t_m) \end{bmatrix} \tag{2.1}$$

$$\begin{bmatrix} \Phi_1(t) & \Phi_2(t) & \cdots & \Phi_n(t) \end{bmatrix} \begin{bmatrix} \gamma_1 \\ \gamma_2 \\ \vdots \\ \gamma_n \end{bmatrix} = G_{interp}(t) \tag{2.2}$$

Where: $\Phi_n$ = basis function $n$, $\gamma_n$ = fitted basis function coefficient $n$,

$BG_{meas}(t_m)$ = BG measurement at time $t_m$, $n$ = number of basis functions,

$m$ = number of BG measurements, $G_{interp}(t)$ = interpolated BG trace

*1st Order B-spline BFs*: The BG interpolation trace is made from a linear combination of 1st Order B-spline BFs. 1st Order B-spline BFs are based on the piece-wise function defined in [222]. When $k = 1$ the equation becomes:

$$\Phi_i(t) = \begin{cases} \frac{t - KW \times i}{KW} & KW \times i < t < KW \times (i+1) \\ 1 - \frac{t - KW \times (i+1)}{KW} & KW \times (i+1) < t < KW \times (i+2) \\ 0 & Otherwise \end{cases} \tag{2.3}$$

Where: $\Phi_i$ = basis function i, $KW$ = knot width, $i$ = basis function number

*2nd Order B-spline BFs*: The BG interpolation trace is made from a linear combination of 2nd Order B-spline BFs, again using the piece-wise function in [222]. When $k = 2$ the equation becomes:

$$\Phi_i(t) = \begin{cases} \frac{(t - KW \times i)^2}{2 \times KW^2} & KW \times i < t < KW \times (i+1) \\ \frac{-1}{KW^2}(KW \times (i + \frac{3}{2}) - t)^2 + \frac{3}{4} & KW \times (i+1) < t < KW \times (i+2) \\ \frac{(KW \times (i+3) - t)^2}{2 \times KW^2} & KW \times (i+2) < t < KW \times (i+3) \\ 0 & Otherwise \end{cases} \tag{2.4}$$

$$\sum_{i=1}^{n} \Phi_i(t) = 1 \ \forall t \tag{2.5}$$

Where: $\Phi_i$ = basis function i, $KW$ = knot width, $i$ = basis function number

$n$ = number of basis functions

The B-spline BFs are in fixed locations, occurring every instance of the chosen KW, and overlap. The inherent property of the B-spline BFs in Eq. (2.5) ensures no underlying waveform can be induced into the fitted data and a constant value can also be represented. An illustrative example of the fitted interpolation techniques can be seen in Fig. 2.2.

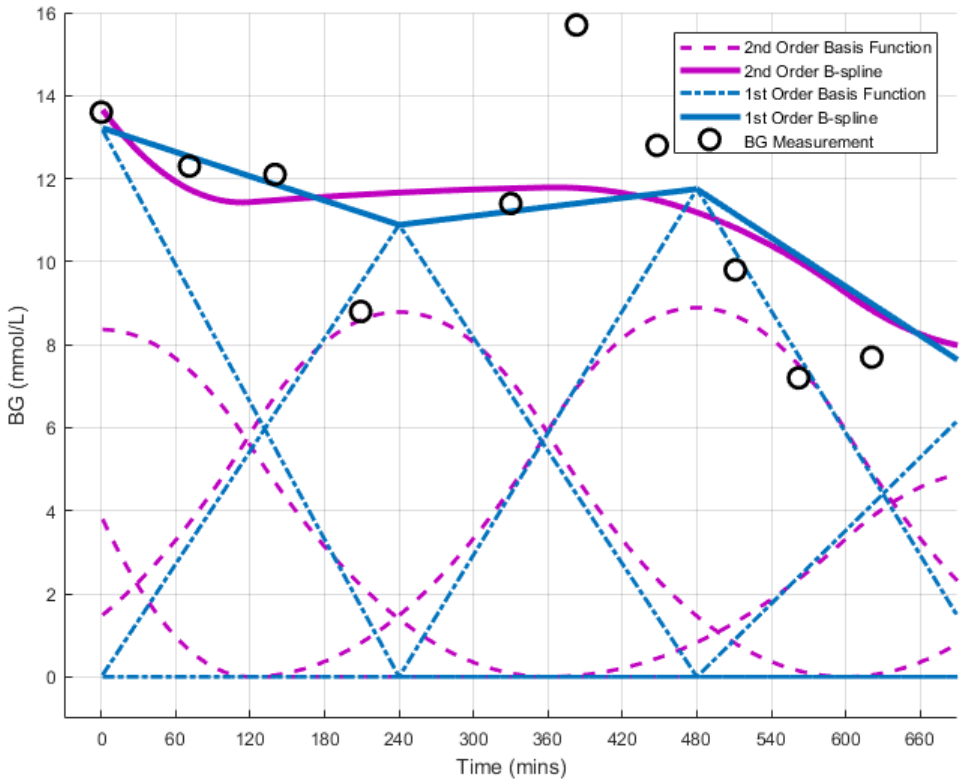



Figure 2.2: Example of the fitted interpolation techniques (1st and 2nd Order B-spline BFs) being investigated.

### 2.2.3 Interpolation Analysis

To assess which interpolation technique best represents the overall BG dynamics, both the fit to the measured and intermediate BG dynamics needs to be considered. To achieve this goal, a proportion of BG measurements are removed from the dense SPRINT BG measurement sets before interpolation. The removed BG measurements are then compared to the post-interpolation BG estimate for independent validation. Clinical patient BG data was thinned to create 2, 3 and 4 hour periods between measurements, similar to what would be expected clinically from STAR [215] and many other protocols [101], [109], [129], [213], [214].

Removed BG measurements are referred to as *'hidden'* measurements, and the remaining measurements *'observed'* measurements. For a BG measurement to be removed it must meet the following criteria:

1. Can be removed without causing a gap between the neighbouring measurements greater than the measurement period being investigated (2, 3 and 4 hours).
2. The interventions (nutrition and insulin) given to the patient over this period are constant. Intervention changes would only be able to be captured by a model and would not usually occur without a prior BG measurement.

An example of this removal process is shown in Fig. 2.3, and Table 2.1 summarises the resulting sparse SPRINT BG data.

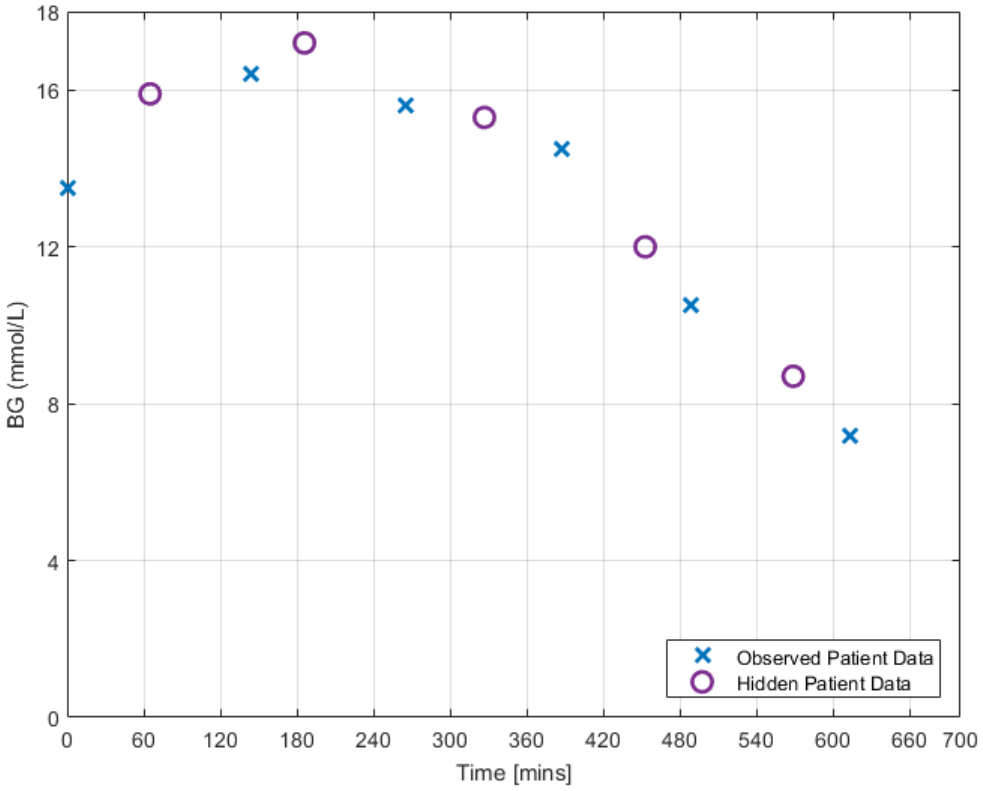



Figure 2.3: Example of BG measurement removal from patient data to maximize 2 hour BG measurement intervals.

Table 2.1: Thinned patient data sets for each measurement interval to be used for evaluation of techniques.

| Measurement interval | 2 hr | 3 hr | 4 hr |
|---|---|---|---|
| No. Patients | 29 | 31 | 34 |
| No. Observed Meas. | 3296 | 2922 | 1862 |
| No. Hidden Meas. (% Total) | 853 (20.6%) | 1404 (32.5%) | 2512 (57.4%) |

All interpolation techniques are investigated in regard to goodness of fit of both the observed and hidden data. A range of BF KWs are used for the fitted interpolation techniques, based on Eq. (2.3) and Eq. (2.4). Goodness of fit is assessed by using Root Mean Square Error (RMSE) between the interpolated trace and the observed and/or hidden measurements. There is no observed measurement error for the piece-wise interpolation techniques as the piece-wise functions start and end at the observed measurements, so the hidden measurements are the sole form of validation. For fitted interpolation, hidden measurement RMSE is expected to be larger than the observed measurement RMSE as observed measurements are used in the identification process. The error for hidden measurements validates the ability of the interpolation technique to capture the intermediate BG dynamics over time intervals relevant to GC protocols. The RMSE for both the observed and hidden measurements are then compared to the error expected from the point of care measurement device used in the SPRINT study, Arkray Super-Glucocard$^{TM}$ II glucometer (Arkray, Minnesota, USA), which has a measurement error SD ranging from 0.15–0.56 mmol/L depending on the BG value [223].

### 2.2.4 Sampling Analysis

To assess which sampling rate of the pre-determined interpolated BG trace best captures GC performance, key GC performance statistics are compared with various sampling intervals (1 and 60 minute, and original clinical measurement intervals). The statistics compared are:

- BG mean, median and standard deviation.
- Percentage of time in the targeted range (4.4-8.0 mmol/L).
- Percentage of time BG $<$ 2.2 mmol/L, BG $<$ 4.4 mmol/L, and BG $>$ 10 mmol/L.

The percentage of time above, below or in band statistics can only approximated with the provided data as the percentage of raw or resampled measurements with in a certain range. All sampling of the interpolated BG trace starts from the first BG measurement and is therefore heavily dependent on the interpolation technique used. Non-parametric statistics are used exclusively due to the typically skewed distributions of BG data. P-values were computed using the Mann-Whitney rank-sum test for all continuous data. P-values $<$0.025 are considered statistically significant after Bonferroni correction [224] for multiple comparisons.

## 2.3 Results

### 2.3.1 Piece-wise interpolation

Fig. 2.4 shows the cohort hidden RMSE for the 3 piece-wise interpolation techniques (Linear, Spline and Cubic). Linear interpolation gave the best estimate of the hidden measurements, having a mean RMSE of 0.39 mmol/L across the 3 intervals investigated. As expected, the longer the measurement interval interpolated, the further the interpolated trace deviated from the hidden BG measurements.

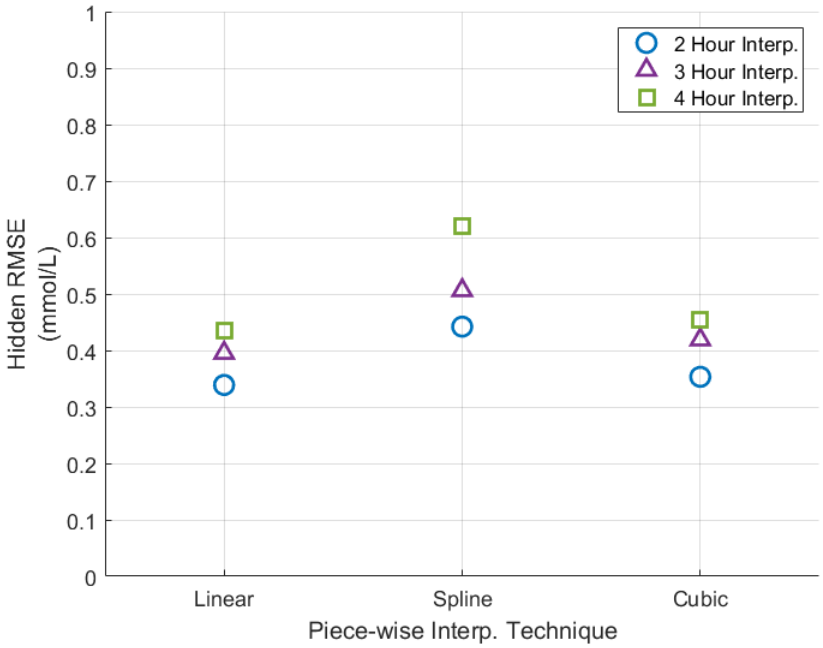



Figure 2.4: Piece-wise interpolation hidden measurement RMSE.

### 2.3.2 Fitted interpolation

Fig. 2.5 and Fig. 2.6 presents the cohort RMSE, for both hidden and observed measurements of the 1st and 2nd order B-spline BFs, respectively. In both figures, as the KW is increased the observed measurement RMSE is shown to increase, while the hidden measurement RMSE decreases.

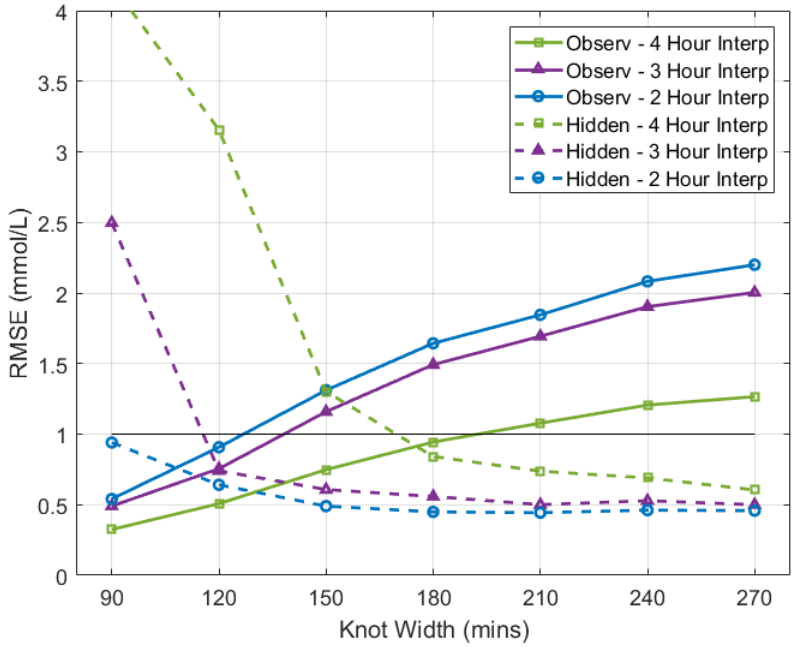



Figure 2.5: 1st Order B-spline BFs fitted interpolation RMSE of observed and hidden measurements. The black line provides reference to the upper limit of Fig. 2.4

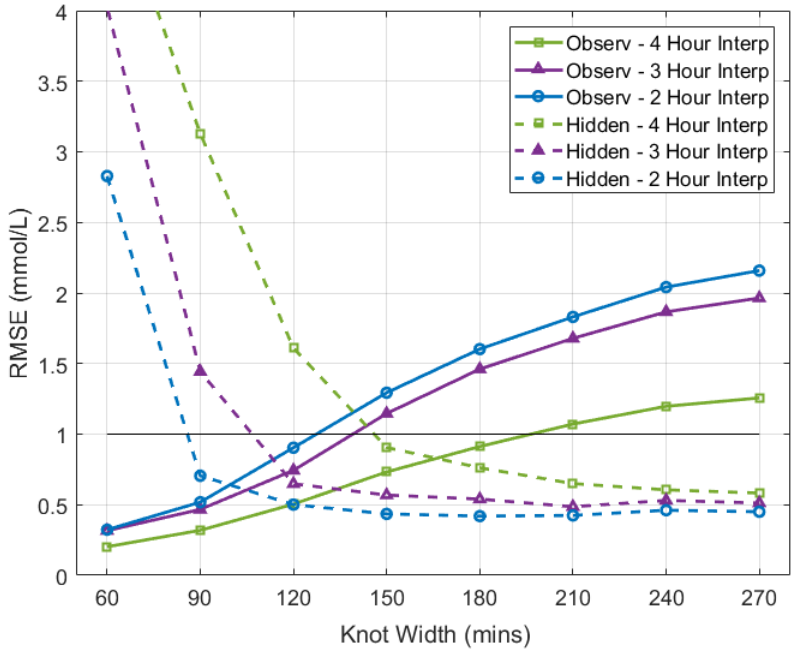



Figure 2.6: 2nd Order B-spline BFs fitted interpolation RMSE of observed and hidden measurements. The black line provides reference to the upper limit of Fig. 2.4

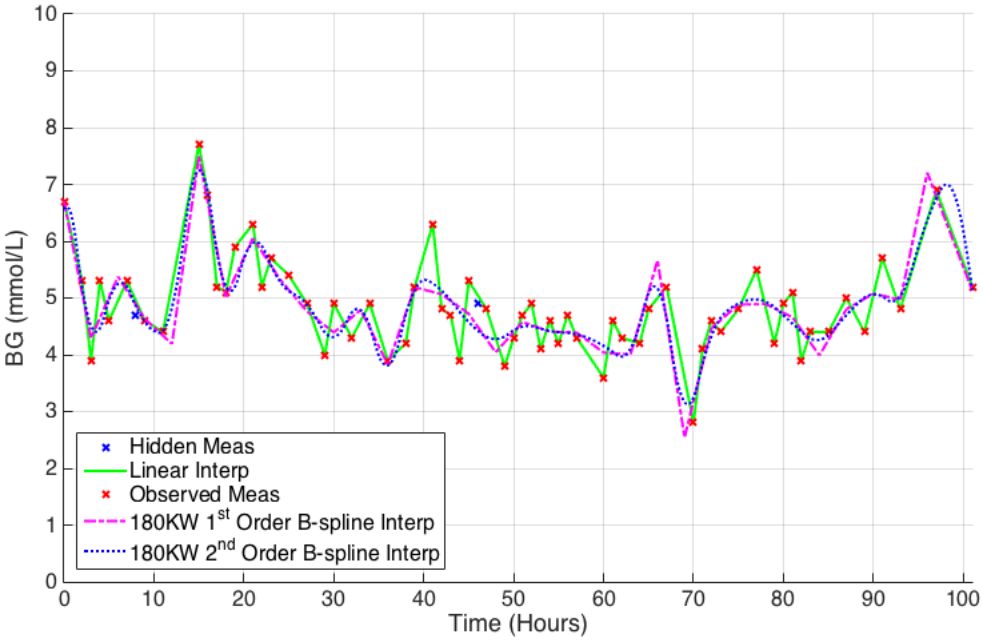



Figure 2.7: Example of the two fitted interpolation techniques fitted to patient data. The linear piece-wise interpolation technique is also provided for comparison

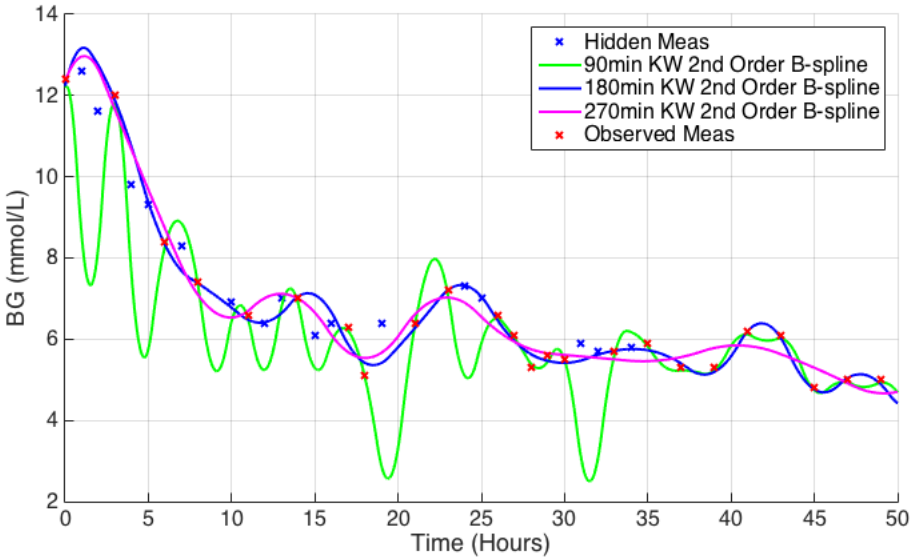



Figure 2.8: Example of the influence of KW on the fitted interpolation fit.

### 2.3.3 Sampling interval

The prior analysis shows linear interpolation provided the best estimate of the intermediate BG dynamics post measurement. Using linear interpolation, the effect of sampling rate on the STAR cohort GC statistics was investigated. Table 2.2 shows the results are significantly skewed if re-sampling is not used. This is likely a result of the raw measurements having different measurement intervals in and out of the targeted 4.4-8.0 mmol/L, as per the STAR protocol. In addition, a slight variation in some statistics are observed if the interpolated BG trace is sampled more frequently.

Table 2.2: GC performance statistics of the STAR GC protocol using different sampling intervals on a linearly interpolated BG trace.

| Sampling Interval | Raw Measurements | Hourly | Minutely | P-Values | |
|---|---|---|---|---|---|
| | | | | Raw vs. Hourly | Hourly vs. Minutely |
| Number patients | 221 | 221 | 221 | - | - |
| Cohort Statistics | | | | | |
| BG Mean | 6.92 | 6.73 | 6.71 | - | - |
| BG Median [IQR] | 6.80 [5.90 - 7.90] | 6.61 [5.96 - 7.40] | 6.60 [5.95 - 7.38] | - | - |
| BG SD | 1.29 | 1.23 | 1.23 | - | - |
| % time <2.2 mmol/L | 0.04328 | 0.00456 | 0.00941 | - | - |
| % time <4.4 mmol/L | 2.62 | 1.35 | 1.32 | - | - |
| % TIB 4.4-8.0 mmol/L | 74.32 | 83.30 | 83.78 | - | - |
| % time >10 mmol/L | 7.13 | 4.10 | 3.88 | - | - |
| Per-patient Statistics | | | | | |
| BG Mean | 6.84 [6.50 - 7.42] | 6.66 [6.36 - 7.21] | 6.64 [6.31 - 7.14] | 0.001 | 0.38 |
| BG Median | 6.70 [6.30 - 7.20] | 6.50 [6.14 - 6.90] | 6.49 [6.14 - 6.87] | 0.001 | 0.80 |
| BG SD | 1.43 [1.08 - 1.98] | 1.17 [0.85 - 1.65] | 1.07 [0.79 - 1.51] | <0.001 | 0.08 |
| % time <2.2 mmol/L | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.18 | 0.18 |
| % time <4.4 mmol/L | 0.00 [0.00 - 5.34] | 0.00 [0.00 - 1.79] | 0.00 [0.00 - 1.49] | <0.001 | 0.09 |
| % TIB 4.4-8.0 mmol/L | 81.50 [66.67 - 90.00] | 88.42 [77.42 - 94.44] | 88.80 [77.89 - 95.52] | <0.001 | 0.37 |
| % time >10 mmol/L | 2.78 [0.00 - 8.70] | 1.22 [0.00 - 5.56] | 0.78 [0.00 - 4.48] | 0.04 | 0.56 |

*blood glucose (BG), standard deviation (SD), inter-quartile range (IQR), time in band (TIB).
Data presented in Median [inter-quartile range (IQR)] where appropriate.

Fig. 2.9 shows how the various resampling techniques influence the interpretation of results. The raw measurements can be seen to be dense at the beginning when the patient is out of the target band slightly sparser within the target band. Hourly resampling can be seen to more fairly capture the underlying BG trace. However, as seen at hour 29, hourly resampling can still miss key peaks in BG, dynamics that could only be captured with minutely resampling.

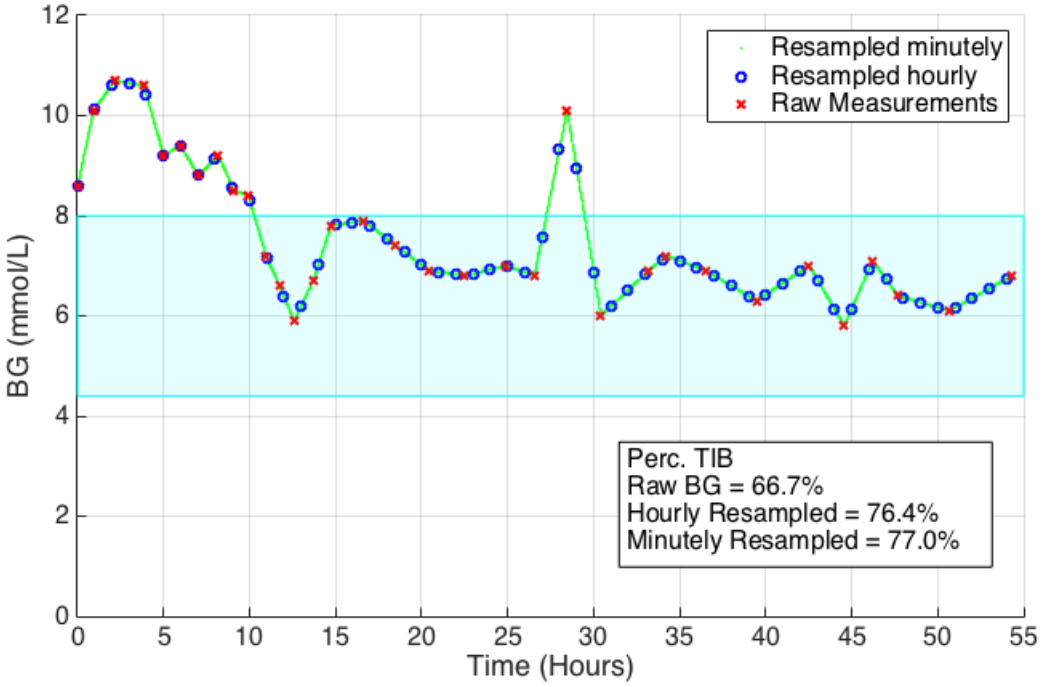



Figure 2.9: Example of the influence of resampling on time in band statistics.

## 2.4 Discussion

### 2.4.1 Piece-wise interpolation performance

Fig. 2.4 shows all the piece-wise interpolation techniques performed extremely well in capturing intermediate BG dynamics. Linear interpolation performed the best with an average RMSE of 0.39 mmol/L, over all the measurement intervals assessed. As the measurement interval assessed increased, so did the hidden RMSE. This result is likely due to the greater time for the intermediate BG dynamics to deviate from the interpolated trace.

### 2.4.2 Fitted interpolation performance

Fig. 2.5 and Fig. 2.6 show a trade-off of error to the the hidden and observed measurements for the fitted interpolated trace. As the KW is increased, the RMSE of the observed measurements is increased, while the RMSE of the hidden measurements is decreased. This is due to fitted interpolation techniques becoming less erratic as the BG KW increases, as shown in Fig. 2.8. The KW BF which provided the most similar magnitude hidden and observed RMSE was chosen as the optimal, equally representing both hidden and observed measurements. The 150 minute KW 1st order B-spline BF provided the best compromise of fit to the observed (mean RMSE 1.07 mmol/L) and hidden (mean RMSE 0.80 mmol/L) measurements. Similarly, the 150 minute KW 2nd order B-spline BF also provided the best compromise of fit to the observed (mean RMSE 1.06 mmol/L) and hidden (mean RMSE 0.64 mmol/L) measurements. Note as the variability BG levels increased the fitted interpolation techniques struggled to capture the erratic dynamics as seen in Fig. 2.7. The restrictive nature of fitting wide knot-width basis functions is shown by the increase in observed measurement error. Overall, the 2nd order B-spline BF interpolation provided the best fit to both the observed and hidden measurements.

### 2.4.3 Optimal Interpolation

Although the piece-wise interpolation techniques are very prone to erroneous measurements compared to the fitted interpolation techniques, which are designed to incorporate measurement error, they still provided a better estimation of the hidden measurements. The trade-off of fit between observed and

hidden measurements resulted in a much larger RMSE overall for the fitted interpolation techniques compared to the piece-wise interpolation techniques. In addition, the SPRINT BG values were measured using a Super Glucocard II (Arkray, Minnesota, USA), which has a measurement error SD ranging from 0.15–0.56 mmol/L depending on the BG value [223]. Only the linear and cubic piece-wise interpolation techniques provided a RMSE within this measurement error, providing a further independent validation that the piece-wise interpolation techniques provided the best estimation of the intermediate BG dynamics.

### 2.4.4 Sampling Analysis

Table 2.2 clearly shows there are significant differences in key GC statistics when using raw measure -ments compared to a sampled interpolated BG trace, for both cohort and per-patient statistics. The largest impact was seen in the median per-patient percentage of time statistics; 81.5% vs 88% BG within 4.4-8.0 mmol/L, $P < 0.001$; 2.78% vs approximately 1.0% BG $> 10.0$ mmol/L, $P = 0.04$. A significant difference can also be seen in the per-patient BG mean and median (mean BG of 6.84 vs 6.65 mmol/L, $P = 0.001$, and median BG of 6.7 vs 6.49 mmol/L, $P = 0.001$). This discrepancy is most likely due to the varying measurement frequency in and out of band for the STAR GC protocol, inherently causing higher numbers of raw measurements to occur outside of the targeted band than within. This behaviour is common in GC protocols [101], [109], [129], [213], [214] and would result in *'poor'* measurements being over-represented, skewing statistics.

Only a small benefit is observed from sampling the interpolated BG trace minutely compared to hourly. The largest difference occurring in the per-patient median percentage of time BG $> 10$ mmol/L measurements (0.78% vs 1.22%, $P = 0.56$ Table 2.2). This result is most likely due to the hourly sampling of the interpolated BG trace not capturing the peaks in BG seen with minutely sampling. This outcome is especially important when considering the number of patients within the hyper- and hypo- glycaemic regions (BG $> 10.0$ mmol/L and BG $< 4.4$ mmol/L). In regard to the other statistics, a negligible difference in BG mean, and median was seen, Table 2.2. However, a slight difference could be seen in the per-patient standard deviation of BG between sampling rates (1.17 vs 1.07, $P = 0.08$). Again,this result is likely due to the hourly sampling rate not capturing

the full spread of the BG trace. Overall, minutely sampling had limited effect on central tendency statistics, and a greater impact on outlying events or surges, as expected.

### 2.4.5 Limitations

The SPRINT protocol has measurement intervals of 1-2 hours [101]. Thus, as per protocol, the SPRINT BG data is denser in regions where a patient is variable and/or out of the targeted band. Therefore, the measurements removed (hidden measurements) to make the data sparse are more likely to be removed from the more variable and out of band BG regions (BG $<$ 4.4 mmol/L and BG $>$ 6.1 mmol/L). Hence, the hidden measurement error is a stronger validation test, but will likely have higher associated BG measurement error than if more stable periods were included. The results are thus a conservative estimate.

The number of observed and hidden BG measurement varies as the measurement interval assessed is increased due to the SPRINT data needing to be denser to assess smaller measurement intervals. However, there is still a significant amount (20.6%) of data for assessment of the 2 hour measurement interval to provide a fair assessment of the BG interpolation techniques.

## 2.5 Summary

Overall the linear piece-wise performed the best of all interpolation techniques investigated (mean RMSE 0.39 mmol/L), providing the best estimate of the intermediate BG dynamics. The fitted interpolation techniques failed to capture the hidden BG measurements without providing a poor fit to the observed measurements. Thus, linear interpolation provides the best estimate of intermediate BG dynamics and should be used when approximations are required in modelling.

There is a significant difference in key GC performance statistics when comparing raw to resampled interpolated BG measurements, especially when the GC protocols being investigated have varying measurement intervals depending on the BG value. Therefore, for fair comparison of a GC protocol's performance, minutely resampled linear interpolation of BG results is the best option.

# Chapter 3

# Evaluation and simplification of STAR's stochastic model

## 3.1 Background

A feature of the STAR GC protocol is its ability to account for inter- and intra- patient variability of hour-to-hour changes in patient specific $S_I$. STAR captures this variability by using a cohort based stochastic model [145], [149] of 1, 2, and 3 hourly changes in the ICING model-based $S_I$ [148] to compute optimal insulin and nutrition interventions. The cohort based stochastic model enables STAR to generate/predict a 90% range of BG outcome for a given intervention [128], [147]. STAR uses this risk-based MPC technique to maximise time in the targeted band (4.4-8.0 mmol/L), and concomitantly maximise nutrition delivered, while maintaining a maximum 5% risk of BG $<$ 4.4 mmol/L [128], [147].

The insulin and nutrition treatments given by STAR are thus clearly dependent on the predicted $5^{th}$ and $95^{th}$ percentile $S_I$ bounds given by the stochastic model [128], [147]. As a result, the stochastic model bounds directly determine STAR's ability to provide safe and effective GC. If the stochastic bounds are too wide, STAR over estimates patient variability, and, as a result, provides

[1] G. M. Shaw, **K. W. Stewart**, J. Dickson, C. Pretty, and J. G. Chase, "THE SECRET TO SAFE, EFFECTIVE AND SUCCESSFUL INSULIN DOSING," in 41st ANZICS/ACCM INTENSIVE CARE ASM, 2016, p. 281.

[2] **K. W. Stewart**, J. Dickson, C. Pretty, G. Shaw, and J. G. Chase, "Variability is a constant! Insulin sensitivity and its variability in 4 ICU Cohorts.," in 16th Annual Diabetes Technology Meeting, 2016.

too conservative and thus less or ineffective GC. Alternatively, if the stochastic bounds are too narrow, STAR under estimates patient variability, and, as a result, provides too aggressive and thus unsafe GC. Hence, a balance exists in which the stochastic model provides equally effective and safe GC for every patient.

The original controller stochastic model used by STAR [145] was developed using the ICING model published by Lin et al. [148] and a selection of 120 patients from the SPRINT cohort [101]. The stochastic model was built using two dimensional kernel density estimation. $S_I$ was bounded to physiological limits of $1.0\times10^{-5}$ and $1.0\times10^{-3}$ L/(mU.min) [225], [226], which is at the low end of values reported for healthy and pre-diabetic individuals ($1.4\times10^{-4}$ - $4.0\times10^{-3}$ L/(mU.min) [72], [227]). The variance of each point was determined by the local data density in a centred, ortho-normalised space [145]. However, since the creation of this stochastic model further unpublished iterations have been made expanding the limits of the controller stochastic model to $1.0\times10^{-7}$ - $2.8\times10^{-3}$ L/(mU.min) to account for patients with a much higher or lower [72], [227] and possibly more variable $S_I$ [125], [228].

Since the development of the original stochastic model, the physiological model used to describe $S_I$ has progressed (Section 1.2.4.1 *ICING Model*) and an order of magnitude more patient data has been collected across differing demographics and clinical practices. Therefore, to ensure STAR's controller stochastic model captures the required patient variability, and is thus able to provide generalizable safe and effective GC, the currently used controller stochastic model requires comparison to the patient variability seen across differing cohort demographics and clinical practices.

In addition, the *'variability'* in the defined stochastic model bounds appear to be very specific to the cohort of data used to create the stochastic model. Therefore, simplification of the controller stochastic model in the form of a piece-wise polynomial may better approximate the underlying population stochastic bounds. However, validation of the piece-wise polynomials used is required to ensure patient GC performance and safety is not compromised.

The aim of this chapter is to compare the stochastic model currently used by STAR to that of 3 different STAR cohorts, from differing demographics and clinical practices. In addition, a simple piece-wise polynomial approximation of STAR's currently used controller stochastic model is proposed and its GC performance and safety investigated in virtual trials.

## 3.2 Methods

### 3.2.1 Insulin Sensitivity identification

A variant of the clinically evaluated ICING model [31], [148] is used to describe glucose-insulin metabolic system dynamics, Section 1.2.4.1 *ICING Model*. The model-based $S_I$ represents the whole body balance of insulin and glucose from all sources, where $S_I$ is identified through integral-based identification [148], [153]. Note, considering that $S_I$ is mathematically identified to best fit the BG measurements, any measurement error or discrepancies in the given and STAR recorded interventions can lead to excessively high or erratic $S_I$ values. The minimum value of $S_I$ is limited to $1{\times}10^{-7}$ L/(mU.min), approximately 1,000x lower than the $S_I$ identified for healthy and pre-diabetic subjects [72], [227].

### 3.2.2 Stochastic model generalizability

To validate the $5^{th}$ and $95^{th}$ percentile bounds of the stochastic model currently used by STAR, the bounds are compared to the $5^{th}$ and $95^{th}$ percentile bounds of 3 different STAR cohort's stochastic models. The ability for the current stochastic model to capture each cohort's $S_I$ variability is assessed via a histogram of the percentage of $S_I$ values within the current STAR $5^{th}$ and $95^{th}$ percentile bounds, ideally 90%. Each of the STAR cohort stochastic models are formed using the same methodology as described by Lin et al. [145]. Note, only the 1 hour stochastic model is compared as this model has the largest influence on control, and models of the other intervals are similar. Also, only the $5^{th}$ and $95^{th}$ percentile values are compared, as these are what are used in STAR's GC algorithm.

Each of the cohort's absolute $S_I$ value CDFs are also compared. Due to the large number of $S_I$ values identified, most statistical tests comparing the cohorts values (Wilcoxon rank-sum or Kruskal-Wallis

test) will return a very small P value, regardless of actual similarity or differences. Therefore, only visual inspect is used to compare each of the cohorts CDFs.

#### *3.2.2.1 Patient Data*

Clinical data from 3 cohorts treated with the STAR protocol [128], [229] in Christchurch Hospital ICU, Christchurch, NZ, Kálmán Pándy Hospital ICU, Gyula, Hungary, and the International Medical University Medical Centre, Kuantan, Malaysia from 2011 to present were used for stochastic model comparison. Details of these patients are shown in Table 3.1. The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of the Christchurch Hospital ICU data. According to the local ethical codes in Hungary and Malaysia, the retrospective study is considered a clinical data audit, and only required depersonalization of data without the need for individual patient consent to analyse or publish the anonymized data.

Table 3.1: Patient Demographics for the 3 STAR cohorts being used for comparison of stochastic models. Note, not all data is available for all cohorts.

| Cohort | STAR Gyula | STAR Christchurch | STAR Kuantan |
|---|---|---|---|
| Number Patients | 47 | 426 | 36 |
| Age | 66 [58 - 71] | 65 [55 - 72] | 62 [55 - 68] |
| Percent male | 61.7 | 63.6 | 61.1 |
| Length of ICU Stay (Days) | 14.0 [8.0 : 20.5] | 4.6 [2.0 - 11.6] | - |
| Mean Days on protocol | 5.3 | 3.8 | 3.9 |
| APACHE II Score | 32.0 [28.0 : 36.0] | 20.00 [15.00 - 25.00] | - |
| ICU Mortality (%) | 38.3 | 20.9 | - |
| Percent T2DM | 0.0 | - | 63.9 |

*Intensive Care Unit (ICU), Acute Physiology And Chronic Health Evaluation (APACHE), Type 2 Diabetic (T2DM). Data presented in Median [inter-quartile range (IQR)] where appropriate.

### 3.2.3 Stochastic model simplification

Each of the 1, 2 and 3 hour STAR controller stochastic models are approximated by piece-wise polynomials. The mathematical approximations of the stochastic model bounds were chosen to be as simple as possible, while still being representative of the stochastic model trends. Due to 99% of $S_I$ values being less than $1.8\times10^{-3}$, any stochastic model characteristics above this value were considered to be unrepresentative of the underlying population trends. In addition, the mathematical approximations were desired to follow the previous stochastic model trends where data density was high. Therefore, 2nd order piece-wise polynomials were used to the represent the $5^{th}$ and $95^{th}$

percentile bounds. The correlation coefficients of the piece-wise polynomial approximations to the current stochastic model bounds below $1.8\times10^{-3}$ are used to assess representation of currently used stochastic model bounds. A comparison of the piece-wise polynomials and the the current controller stochastic models are shown in Figures 3.1 to 3.3. Note, the piece-wise polynomial stochastic models have no upper bound, unlike the currently used stochastic models which saturate $S_I$ values at their upper bound ($2.8\times10^{-3}$).

The ability for the piece-wise polynomials to capture the patient variability is investigated through virtual trials [154], [230]. Clinical data from the 426 patients treated with STAR in Christchurch, Table 3.1, were used to generate virtual patients. Virtual patients were created from the patient-specific time varying model-based $S_I$ profiles [153]. This model-based $S_I$ can be used as a critical marker of a patient's metabolic state [145], [230]. These virtual patients allow robust protocols to be safely designed and rigorously tested prior to clinical implementation, improving patient safety and minimising the need for protocol alterations post-implementation [154], [230]. The virtual patients were simulated with the stochastic models of interest, the STAR GC protocol, and the ICING model. From the virtual trial results of the two sets of stochastic models, currently used and piece-wise polynomial approximation, the GC safety and performance is compared.

#### *3.2.3.1 1 hour stochastic model*

The polynomials are defined:

$$S_{I,n+1}\ 5^{th}\ perc = \begin{cases} 1 \times 10^{-7} & S_{I,n} < 6 \times 10^{-5} \\ -150.8 \times {S_{I,n}}^2 + 0.7459 \times S_{I,n} - 2.915 \times 10^{-5} & 6 \times 10^{-5} \leq S_{I,n} \leq 2.5 \times 10^{-3} \\ 0.89 \times 10^{-3} & 2.5 \times 10^{-3} < S_{I,n} \end{cases} \tag{3.1}$$

$$S_{I,n+1}\ 95^{th}\ perc = \begin{cases} 2.8 \times 10^{-4} & S_{I,n} < 1 \times 10^{-4} \\ 401.1 \times {S_{I,n}}^2 + 0.8108 \times S_{I,n} + 1.98 \times 10^{-4} & 1 \times 10^{-4} \leq S_{I,n} \end{cases} \tag{3.2}$$

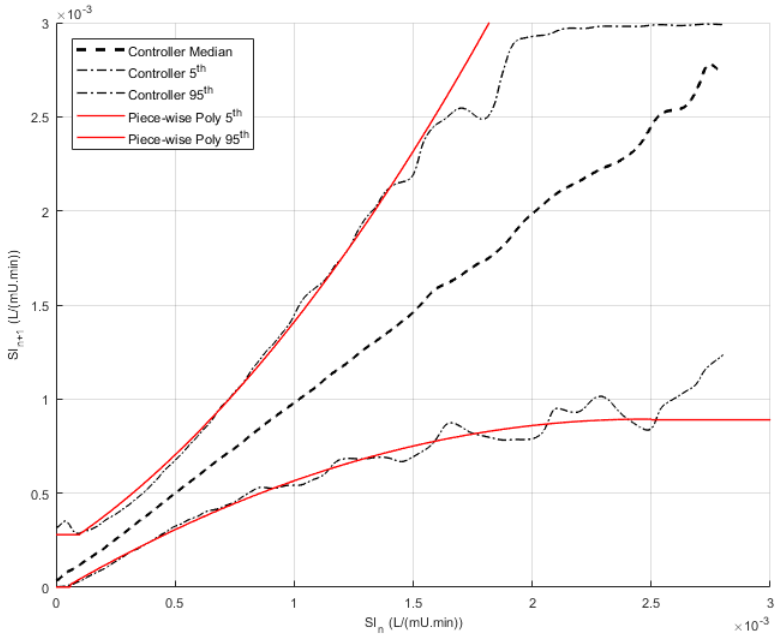



Figure 3.1: A comparison of the 1 hour controller stochastic model and piece-wise polynomial approximation.

#### *3.2.3.2 2 hour stochastic model*

The polynomials are defined:

$$S_{I,n+2}\ 5^{th}\ perc = \begin{cases} 1 \times 10^{-7} & S_{I,n} < 6 \times 10^{-5} \\ -158.2 \times {S_{I,n}}^2 + 0.7459 \times S_{I,n} - 2.915 \times 10^{-5} & 6 \times 10^{-5} \leq S_{I,n} \leq 2.2 \times 10^{-3} \\ 0.84 \times 10^{-3} & 2.2 \times 10^{-3} < S_{I,n} \end{cases} \tag{3.3}$$

$$S_{I,n+2}\ 95^{th}\ perc = \begin{cases} 2.8 \times 10^{-4} & S_{I,n} < 1 \times 10^{-4} \\ 474.5 \times {S_{I,n}}^2 + 0.8108 \times S_{I,n} + 1.98 \times 10^{-4} & 1 \times 10^{-4} \leq S_{I,n} \end{cases} \tag{3.4}$$

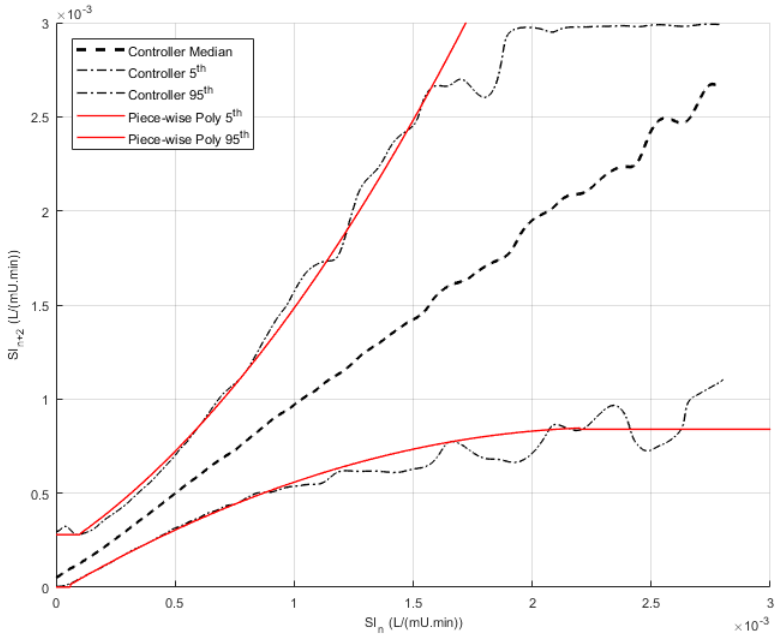



Figure 3.2: A comparison of the 2 hour controller stochastic model and piece-wise polynomial approximation.

#### *3.2.3.3 3 hour stochastic model*

The polynomials are defined:

$$S_{I,n+3}\ 5^{th}\ perc = \begin{cases} 1 \times 10^{-7} & S_{I,n} < 6 \times 10^{-5} \\ -167.5 \times {S_{I,n}}^2 + 0.7459 \times S_{I,n} - 2.915 \times 10^{-5} & 6 \times 10^{-5} \leq S_{I,n} \leq 2.2 \times 10^{-3} \\ 0.8 \times 10^{-3} & 2.2 \times 10^{-3} < S_{I,n} \end{cases} \tag{3.5}$$

$$S_{I,n+3}\ 95^{th}\ perc = \begin{cases} 2.8 \times 10^{-4} & S_{I,n} < 1 \times 10^{-4} \\ 557.9 \times {S_{I,n}}^2 + 0.8108 \times S_{I,n} + 1.98 \times 10^{-4} & 1 \times 10^{-4} \leq S_{I,n} \end{cases} \tag{3.6}$$

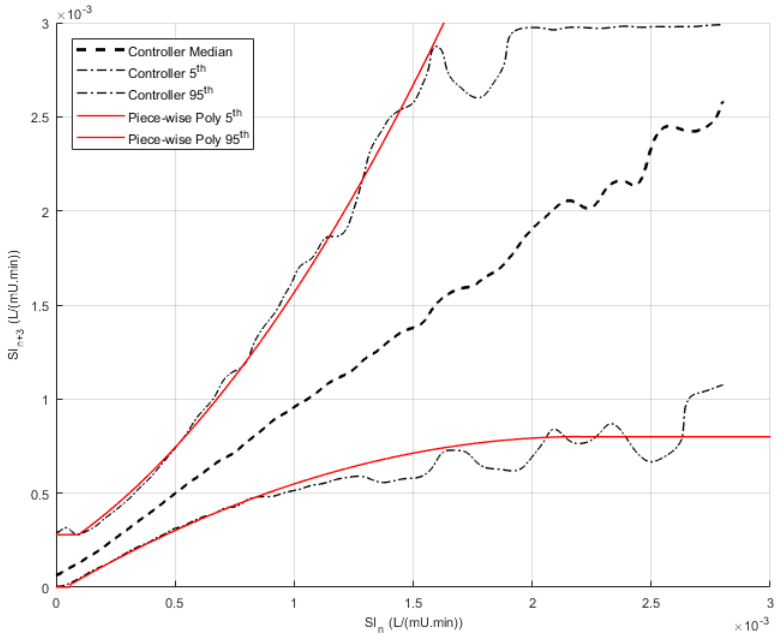



Figure 3.3: A comparison of the 3 hour controller stochastic model and piece-wise polynomial approximation.

#### *3.2.3.4 Analysis and Statistics*

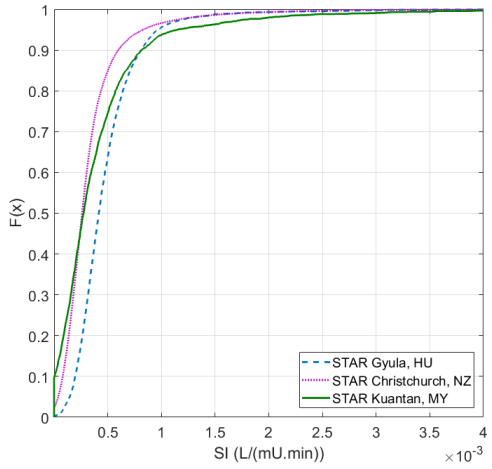
Due to irregular sampling intervals, patient episode BG data were analysed after linear interpolation at 60 min intervals, see Chapter 2 *Interpretation of Retrospective BG Measurements*. Note, minutely sampling was not used as this analysis was preformed before the prior chapter's analysis had been performed. Mean hourly nutrition rates of glucose are reported, but exclude hours in which patients were not fed, as occasionally patients could not be fed due to clinical reasons irrespective of the GC protocol.

Non-parametric statistics are used exclusively for all the comparative tests due to the typically skewed distributions of BG, insulin dose and other data. P-values were computed using the Mann -Whitney rank-sum test for all continuous data and the chi-squared test for categorical data. P-values $<0.05$ are considered statistically significant.

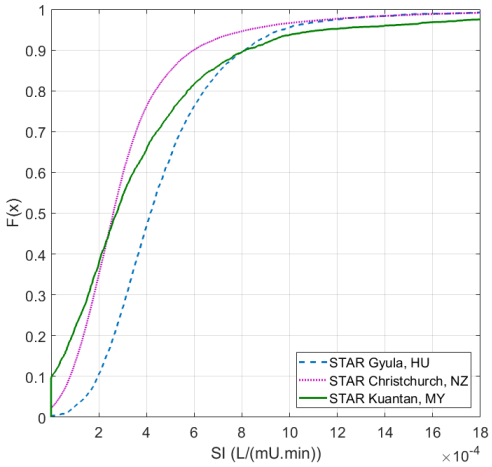
## 3.3 Results

### 3.3.1 Stochastic model generalizability

Fig. 3.4 shows the $S_I$ CDFs for all 3 of the STAR cohorts are very different. The median values range from approximately 2.7e$\times 10^{-4}$ L/(mU.min) for Christchurch and Kuantan to 4.2$\times 10^{-4}$ L/(mU.min) for Gyula. In addition, each cohort has varying amounts of saturation occurring ($S_I = 1\times 10^{-7}$), with levels of 0.3%, 2.3%, and 9.5% for Gyula, Christchurch and Kuantan, respectively. This result may indicate variability in the ICING model's ability to capture metabolic dynamics across cohorts. These results all also show the absolute $S_I$ differences possible between cohorts.




(a) Overall CDFs.




(b) Zoomed in to the $99^{th}$ percentile $S_I$ value ($1.8\times 10^{-3}$).

Figure 3.4: The cumulative distribution function (CDF) of insulin sensitivity ($S_I$) for the 3 STAR cohorts investigated.

Figs. 3.5 and 3.6 shows the controller stochastic model to capture the majority of patient $S_I$ variability (shaded $5^{th}$-$95^{th}$ percentile region) in both Gyula and Christchurch. Equally, the percentage of identified $S_I$ values within the controller stochastic model's $5^{th}$-$95^{th}$ percentile bounds are consistently equal to or greater than 90%, where data is dense ($S_I < 1.0{\times}10^{-3}$). In contrast, the Kuantan cohort's shaded $5^{th}$-$95^{th}$ percentile region, Fig. 3.7 can be seen to well exceed those of the controller stochastic model bounds. In addition, the percentage of identified $S_I$ values within the controller stochastic model's $5^{th}$-$95^{th}$ percentile bounds are consistently below 90%, where data is dense ($S_I < 1.0{\times}10^{-3}$). Thus, suggesting the variability seen in the Kuantan cohort is much larger than STAR currently accounts for.

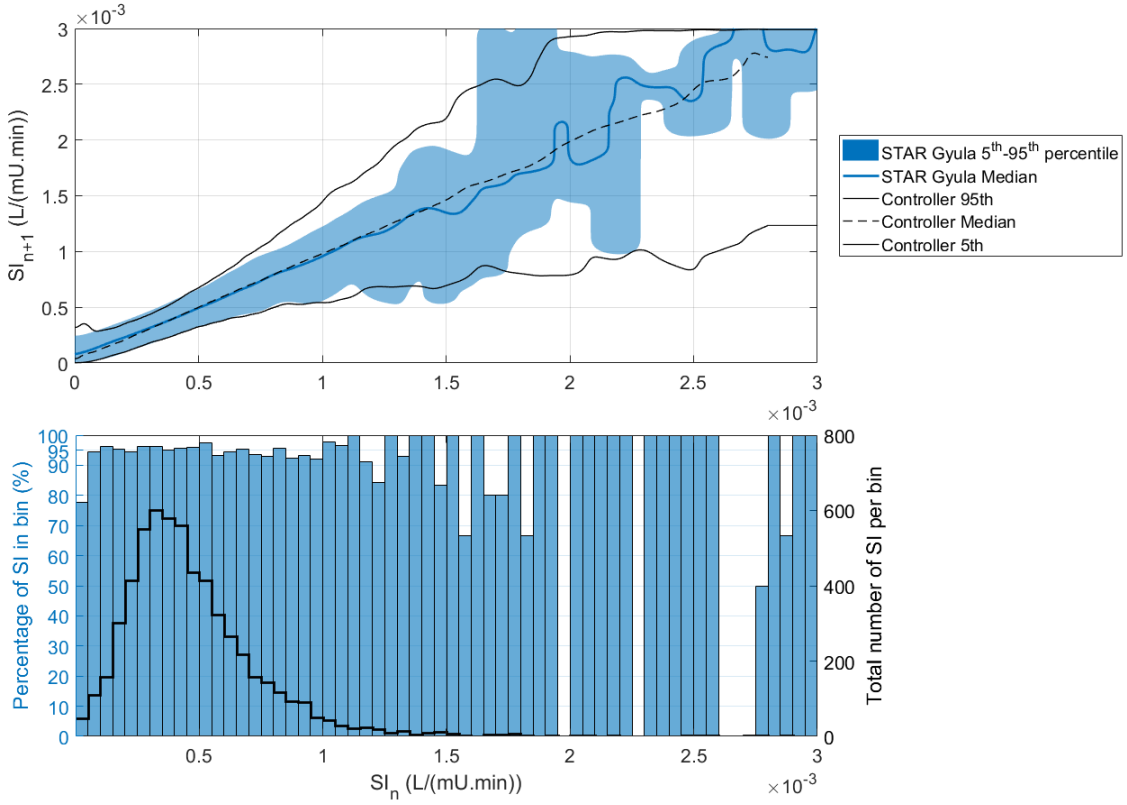



Figure 3.5: (Top) Comparison of the STAR controller and STAR Gyula stochastic model. (Bottom) Histogram of percentage of $S_I$ within the STAR controller $5^{th}$-$95^{th}$ percentile bounds.

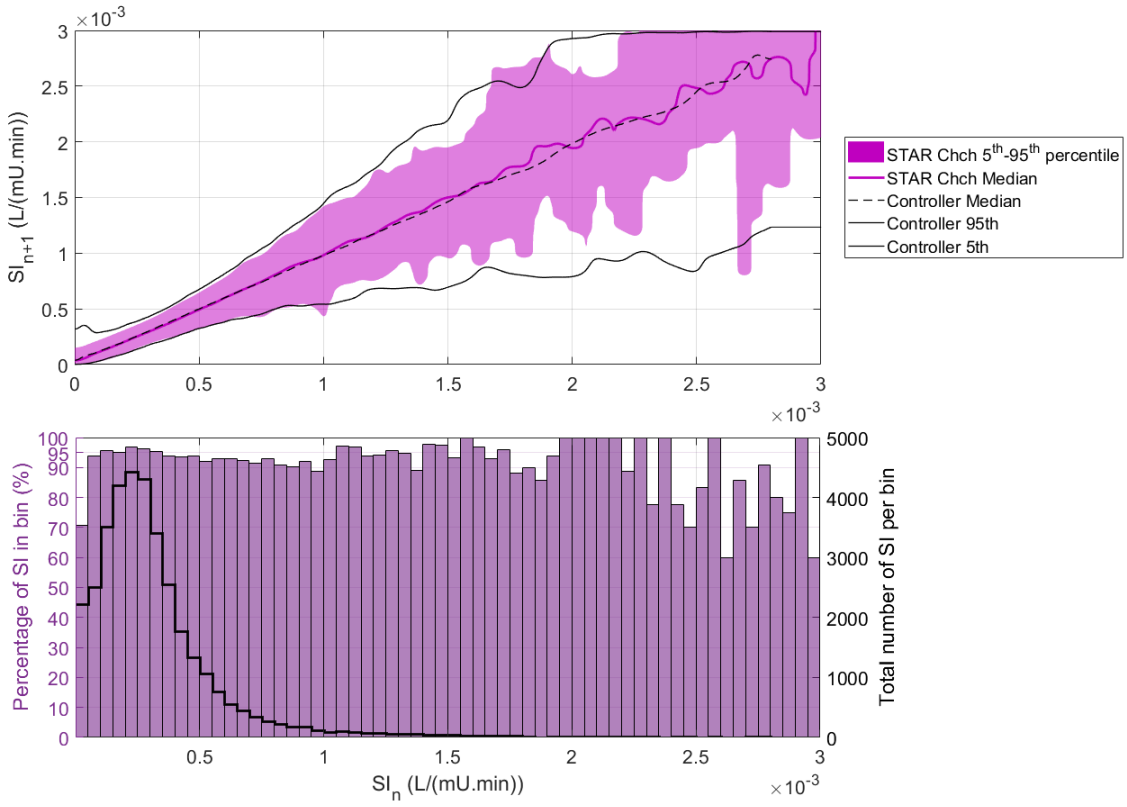



Figure 3.6: (Top) Comparison of the STAR controller and STAR Christchurch stochastic model. (Bottom) Histogram of percentage of $S_I$ within the STAR controller $5^{th}$-$95^{th}$ percentile bounds.

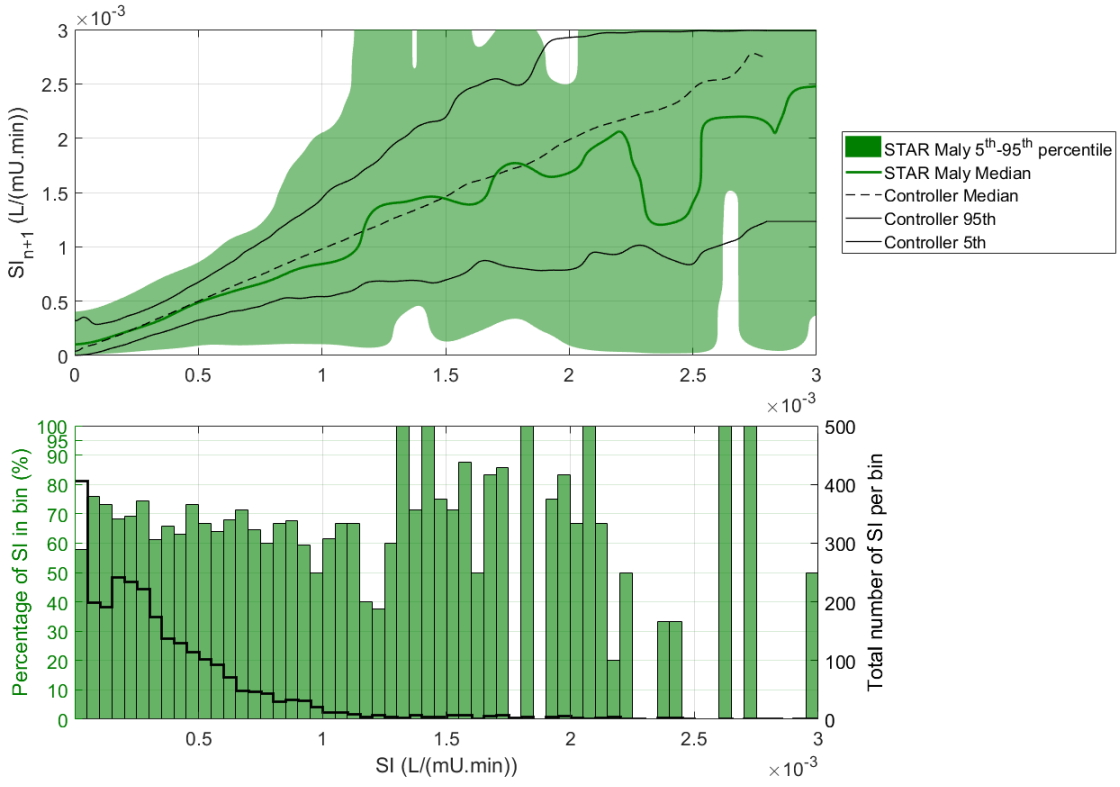



Figure 3.7: (Top) Comparison of the STAR controller and STAR Kuantan stochastic model. (Bottom) Histogram of percentage of $S_I$ within the STAR controller $5^{th}$-$95^{th}$ percentile bounds.

### 3.3.2 Stochastic model simplification

Table 3.2 shows the correlation coefficients of the piece-wise polynomial approximations to the current stochastic model bounds ($S_I < 1.8{\times}10^{-3}$). All of the piece-wise polynomial approximations of the stochastic bounds are shown to have an $R^2$ value $> 0.96$. Overall indicating the simple piece-wise polynomials captured the data and underlying trends in percentiles very well.

Table 3.2: Correlation coefficients ($R^2$) of the piece-wise polynomial approximations to the currently used stochastic model bounds, when $S_I < 1.8{\times}10^{-3}$.

| | Stochastic model | | |
|---|---|---|---|
| | 1 Hour | 2 Hour | 3 Hour |
| 5th percentile approx. $R^2$ | 0.988 | 0.984 | 0.978 |
| 95th percentile approx. $R^2$ | 0.990 | 0.983 | 0.969 |

The GC performance and safety of STAR using the current controller stochastic models and the proposed piece-wise polynomial approximate stochastic models is shown in Table 3.3. The piece-wise polynomial stochastic models provided very similar GC performance to the current-controller stochastic models, with similar time in the targeted 4.4-8.0 mmol/L BG band (87.9% vs. 87.5%, P=0.67) and reduction of hyperglycaemia (% time BG $>$ 10.0 mmol/L, 1.6% vs. 1.7%, P=0.91). Equally, the safety provided by both sets of stochastic models was similar, both having similar numbers of severe hypoglycaemia measurements (BG $<$ 2.22 mmol/L, 9 vs. 8 measurements, P=1.0). Interestingly, the piece-wise polynomial stochastic models slightly improved safety having 19 less measurements of mild hypoglycaemia (BG $<$ 4.0 mmol/L), P = 0.2. The hourly resampled BG CDFs for each set of stochastic models are plotted in Fig. 3.8. Both sets of stochastic models resulted in very similar BG CDFs, again emphasising the approximately equivalent control able to be offered with the piece-wise polynomial stochastic models.

Table 3.3: Comparison of the per-patient virtual trial GC performance and safety results for the STAR controller with the current and proposed piece-wise polynomial stochastic models.

| | STAR Controller | STAR Piece-wise Poly | P-Value |
|---|---|---|---|
| Num Patients | 426 | 426 | - |
| Total hours | 38833 | 38835 | - |
| Num BG measurements | 22485 | 22393 | - |
| Measures/day (Per-Patient) | 14.2 [11.4 - 24.5] | 14.3 [11.4 - 24.5] | 0.92 |
| *GC Performance* | | | |
| BG median (mmol/L) | 6.2 [5.9 - 7.0] | 6.4 [5.9 - 7.1] | 0.04 |
| BG mean (mmol/L) | 6.4 [6.1 - 7.3] | 6.6 [6.1 - 7.4] | 0.08 |
| BG SD (mmol/L) | 1.3 [1.0 - 1.7] | 1.2 [0.9 - 1.7] | 0.59 |
| % BG >10.0 mmol/L | 1.6 [0.0 - 7.7] | 1.7 [0.0 - 7.7] | 0.91 |
| % BG within 4.0-8.0 mmol/L | 87.9 [69.2 - 95.1] | 87.5 [70.6 - 94.6] | 0.67 |
| % BG <4.4 mmol/L | 0.0 [0.0 - 4.8] | 0.0 [0.0 - 4.1] | 0.33 |
| % BG <2.22 mmol/L | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] | 0.81 |
| Mean hourly insulin rate (U/hr) | 3.7 [2.6 - 5.0] | 3.6 [2.5 - 4.8] | 0.09 |
| Mean hourly feed rate (g/hour) | 4.6 [3.8 - 5.5] | 4.8 [4.0 - 5.6] | 0.25 |
| *Safety* | | | |
| Num measures <4.0 mmol/L | 141 | 122 | 0.20 |
| Num measures <2.22 mmol/L | 9 | 8 | 1 |

*Glycemic Control (GC), blood glucose (BG), standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

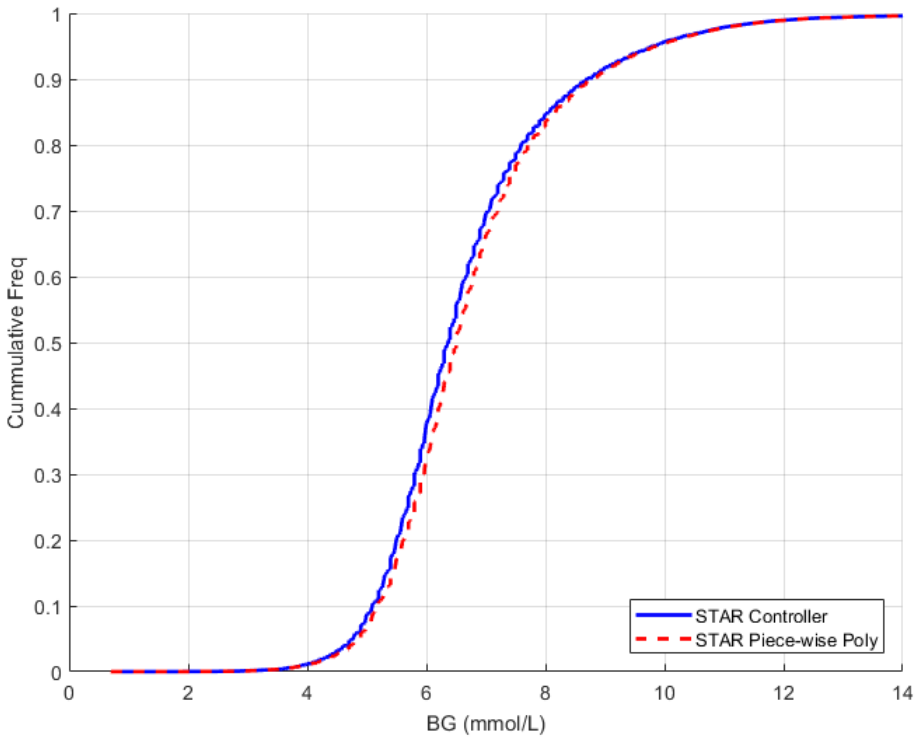



Figure 3.8: Resampled hourly BG cumulative distribution function (CDF) for STAR using the current controller stochastic models and the proposed piece-wise polynomial stochastic models.

## 3.4 Discussion

### 3.4.1 Stochastic model generalizability

The $S_I$ values identified across all of the cohorts investigated were very different in absolute value, as shown by Fig. 3.4. Notably, the Kuantan cohort had the largest spread of $S_I$ values and the highest percentage of $S_I$ saturated values (9.5%), which may be the result of 63.9% of the cohort being type 2 diabetic, as seen in Table 3.1. Overall, the differences in $S_I$ values may be a result of the patient demographics and/or clinical practice resulting in a different identified $S_I$ value.

The currently used 1-hour STAR controller stochastic model's $5^{th}$ and $95^{th}$ percentile bounds captured approximately all of the $S_I$ variability seen in the STAR Gyula and Christchurch cohorts where data was dense ($S_I < 1.0{\times}10^{-3}$), as seen in Figs. 3.5 and 3.6. This shows, within the STAR Christchurch cohort especially where the patient's diabetic status was unknown, the current stochastic model was able to robustly capture the unknown patient variability. In addition, the controller stochastic bounds were observed to actually be over conservative in many cases capturing considerably more than 90% of the identified $S_I$ values, as seen in the histograms of Figs. 3.5 and 3.6. Hence, revealing a potential area of improvement for future iterations of the stochastic model. Note, as the data density decreases ($S_I > 1.0{\times}10^{-3}$) the cohort stochastic model bounds can be observed to become more variable and the controller stochastic model become less representative of this less dense $S_I$ region.

The Kuantan cohort 1-hour stochastic model appeared very different to the STAR controller stochastic model, as seen in Fig. 3.7. At all $S_I$ values, the Kuantan cohort stochastic bounds were wider than the currently used STAR controller stochastic bounds. This is further emphasised by the percentage of identified $S_I$ values within the controller stochastic model's $5^{th}$-$95^{th}$ percentile bounds being consistently below 90%, having mean of approximately 65% where data was dense ($S_I < 1.0{\times}10^{-3}$). This again may be a result of 63.9% of the cohort being type 2 diabetic, Table 3.1, providing a much more metabolically variable cohort. Consequently, when STAR is used in Kuantan it may offer treatment options that are too aggressive for this cohort's typical behaviour. However, STAR

has only been implemented in Kuantan since 2017 on limited patients [231], and, thus, as a result, this data may be very prone to data entry errors or non-compliance.

In addition, as seen in a publication currently under review, adherence to the GC protocol was seen to be very low (approximately 60% at best) due clinical staff not following any recommendations in several cases. Therefore, the recorded interventions of STAR may differ to what was given clinically and, as a result, a much more variable $S_I$ trace is identified. Thus, only once compliance is improved in Kuantan can the stochastic bounds be robustly evaluated.

Given that the STAR controller stochastic model captures both the Gyula and Christchurch cohort well, each from differing clinical practices and demographics, it provides a good basis for the STAR controller in Kuantan until compliance is improved and the *'true'* patient characteristics be better captured. However, compliance in Christchurch was shown to be very high (>86% Chapter 6). Thus, the confidence in the Christchurch data used is very high.

### 3.4.2 Stochastic model simplification

Table 3.2 showed the piece-wise polynomial stochastic models to give a good representation of the currently used stochastic model bounds (All $R^2$ values $> 0.96$). In addition, these piece-wise polynomials were not influenced by the variability in the stochastic model bounds due to low data density, as discussed earlier. Overall indicating the simple piece-wise polynomials captured the current stochastic model bounds well and the underlying trends in percentiles were held at all values of $S_I$.

The piece-wise polynomial stochastic models provided approximately equal GC performance to the currently used controller stochastic models. Both sets of stochastic models provided a very high time in the targeted 4.4-8.0 mmol/L BG band (87.9% vs. 87.5%, P=0.67 Table 3.3) and effectively reduced hyperglycaemia (% time BG $<$ 10 mmol/L, 1.6% vs. 1.7%, P=0.91 Table 3.3). The approximately equivalent GC performance can also be seen by the very similar BG CDFs in Fig. 3.8. In addition, the piece-wise polynomial stochastic models were able to provide slightly safer GC, reducing the incidence of mild hypoglycaemia (BG $<$ 4.0 mmol/L, 141 vs. 122, P=0.2 Table 3.3) and providing

approximately equal occurrences of severe hypoglycaemia (BG $<$ 2.22 mmol/L) measurements (9 vs. 8 measurements, P=1.0 Table 3.3). Overall, these results suggest that the piece-wise polynomial approximation of the controller stochastic models provides a viable alternative without compromising in GC performance or safety.

The reduced number of mild hypoglycaemic cases offered by the piece-wise polynomial stochastic models may be due to capturing the underlying trend in the stochastic model bounds. In particular, the variability in the stochastic model bound, specific to the cohort used to create the stochastic model, is removed and the underlying trend captured. This may have resulted in more representative, and potentially more conservative percentile bounds being provided, reducing the occurrences of mild hypoglycaemia (BG $<$ 4.0 mmol/L) for some patients, Table 3.3.

In addition, since the implementation of STAR, although rare, model-based $S_I$ values of $10.0\times10^{-3}$ L/(mU.min) and upwards have been identified, significantly higher than the bounds of what was first implemented ($1.0\times10^{-3}$ L/(mU.min)) and what is currently implemented in the STAR controller ($2.8\times10^{-3}$ L/(mU.min)). Currently, STAR saturates $S_I$ values at the bounds of the stochastic model which may result in under estimating the $5^{th}$ and $95^{th}$ percentile bounds. However, the piece-wise polynomial stochastic models do not saturate. Therefore, the predicted percentiles, particularly the $95^{th}$ percentile bound, which corresponds to the lower $5^{th}$ percentile BG, will not be under estimated. This may also account for the slight reduction in mild hypoglycaemia seen in Table 3.3.

The piece-wise polynomial stochastic models provide a simple alternative to the currently used STAR controller stochastic model look up tables. In addition, approximating the the $5^{th}$ and $95^{th}$ percentile stochastic bounds with piece-wise polynomials allows stochastic bounds to be better predicted in areas where data density is low, causing the previously formed stochastic to have erratic $5^{th}$ and $95^{th}$ percentile bounds. Hence, the piece-wise polynomials offer a means to better extend these model's functionality.

### 3.4.3 Limitations

Due to $S_I$ being mathematically identified to best fit the BG measurements and clinical data, any measurement error or discrepancies between the interventions given and recorded in STAR could lead to excessively high $S_I$ values. Therefore, the identified $S_I$ value may not be physiologically representative, and is very specific to the model used to identify it. Thus, comparison to other published $S_I$ values, which use different physiological models, has limited validity, and should only be used as guide. However, regardless of the identification process, STAR needs to be able to act appropriately if it is provided very unlikely high $S_I$ value.

The $95^{th}$ percentile piece-wise polynomials are represented by a quadratic in all of the stochastic models, when $S_I > 1.0{\times}10^{-4}$ L/(mU.min). Therefore, the approximated $95^{th}$ percentile will grow to excessively high $S_I$ values when the currently identified $S_I$ value is high, which is likely due erroneous data input. As a result, the $5^{th}$ percentile BG value calculated for any intervention offered by STAR will be very low, and, thus, the intervention recommended by STAR will maximise BG in any way possible. Thus, providing the safest treatment option possible when the identified $S_I$ value is likely erroneous. The improvement in safety with the unbounded piece-wise polynomial stochastic models can be attributed to this safer behaviour at high $S_I$ values. Note, all other approximations of the percentiles are saturated at some value before and after the quadratic used.

As noted, if iterations to the insulin-glucose model used to describe a patient's $S_I$ are made, the stochastic model bounds need to be re-evaluated for the updated model. Thus, the piece-wise polynomial stochastic models will also need to be re-evaluated if this occurs. However, they generalise otherwise.

## 3.5 Summary

The treatment options offered by STAR are very dependent on the $5^{th}$ and $95^{th}$ percentile $S_I$ bounds defined in the stochastic model used. The currently-used stochastic model has been used with STAR in 3 different countries around the world. However, the stochastic bounds in relation to each cohort's stochastic model have not been evaluated. This chapter compared each of the cohort's 1 hour $S_I$ stochastic model to the currently used STAR controller stochastic model.

The $S_I$ variability seen in both Gyula and Christchurch were well captured by the currently used 1 hour STAR controller stochastic model, with the percentage of identified $S_I$ values being consistently equal to or greater than 90% within the controllers current stochastic model bounds. The $S_I$ variability in the Kuantan cohort was seen to be much larger than the what was in the currently used STAR controller stochastic model, with the percentage of identified $S_I$ values being approximately equal 65% within the controllers current stochastic model bounds. However, this discrepancy is likely due to the large non-compliance of data entry in Kuantan and a re-evaluation of the stochastic model is required once compliance is improved.

Piece-wise polynomials were used to approximate the currently used controller stochastic models. The piece-wise polynomial stochastic models were shown to give a good representation of the currently used stochastic model bounds (All $R^2$ values $> 0.96$). GC performance and safety was compared with virtual trials using the STAR Christchurch cohort. The piece-wise polynomials provide approximately equal GC performance and slightly improved safety, having 19 less cases of mild hypoglycaemia (BG $< 4.0$ mmol/L). Overall, the piece-wise polynomial stochastic models provide a promising alternative to the currently used stochastic model.

# Chapter 4

# Improving the identification of model-based Insulin Sensitivity

## 4.1 Background

Some of the most effective and safe GC techniques used currently are model-based [215], [232]–[235], where treatment decisions are based on model identified physiological markers and forward prediction of insulin-glucose response to care. A model that has worked particularly well in guiding GC is the ICING model [148], [158], which is used in the STAR framework [128], [147], [215], [229]. The STAR model-based framework is able to provide patient-specific, safe control using models of time-varying patient metabolic dynamics [145], [149], with discrete, hourly-identified stepwise jumps of model-based $S_I$ values [153], effectively representing $S_I$ with 60 minute KW zeroth order B-spline BF. However, the current identification of $S_I$ has multiple limitations:

- Constant, hourly stepwise jumps in $S_I$ are not strictly physiologically accurate. As BG and thus $S_I$ is a physiological signal, changes should be continuous and smooth [236]–[243], even if rapid, and not discrete step wise jumps.
- Frequent (Hourly) $S_I$ changes require assumed intermediate BG dynamics to be identifiable [244], [245]. As the median patient, mean measurement interval, for STAR is 1.8 hours [215],

[1] **Stewart, K. W.** , Pretty, C. G., Shaw, G. M. and Chase, J. G. (2017) 'Creating Smooth SI. B-spline Basis function representations of insulin sensitivity', Biomedical Signal Processing and Control. (Under Review)

and 2 BG measurements (1 Change in BG per equation) are required to identify each step in $S_I$, linear interpolation is used to assume extra data points required [246], see Chapter 2 *Interpretation of Retrospective BG Measurements*.

- The identified $S_I$ is very susceptible to noise, capturing both measurement noise and modelling error [153]. Rapid $S_I$ changes, caused by large errors, overwhelm relevant model dynamics and thus capture all of the measurement noise.

Therefore, representing $S_I$ with a continuous, identifiable function, which is less susceptible to measurement noise, would significantly improve the physiological representation of this parameter in this already clinically proven model [31], [128], [147], [215].

In many physiological models, the use of orthogonal BFs have proven effective in reproducing physiological signals [247]–[249]. In particular, B-spline BFs have been shown to represent many time varying natural phenomena [250], [251]. Hence, B-spline BFs offer a means of parametrizing a time-varying signal like $S_I$ in a more physiologically relevant and continuous manner, without adding significant complexity to their identification from data [244], [245].

This chapter investigates the identification of the current, zeroth order B-spline BF and an alternative 2nd order B-spline BF in modelling patient-specific time-varying $S_I$. The BFs are compared in terms of physiological relevance, identifiability, and susceptibility to noise and error. The goal is a more physiologically relevant and less *'over fitted'* $S_I$ function that also provides potential for greater physiological insight into metabolic dynamics.

## 4.2 Methods

### 4.2.1 Identification of insulin sensitivity ($S_I$)

A variant of the clinically evaluated ICING model [31], [148] is used to describe glucose-insulin metabolic system dynamics, Section 1.2.4.1 *ICING Model*. The model-based insulin sensitivity, $S_I(t)$, see Eq. (4.1), represents the whole body balance of insulin and glucose from all sources. $S_I(t)$ can be identified through the rearrangement and integration of Eq. (4.1) [148], [153], as shown below.

$$\dot{G}(t) = -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G} \tag{4.1}$$

$$\int_{G_{meas_0}}^{G_{meas_n}} G(t)\ dG = \int_{t_0}^{t_n} -p_G G(t) - S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+EGP-CNS}{V_G}\ dt$$

$$\int_{t_0}^{t_n} S_I(t)G(t)\frac{Q(t)}{1+\alpha_G Q(t)}\ dt = \int_{t_0}^{t_n} -p_G G(t) + \frac{P(t)+EGP-CNS}{V_G}\ dt - (G_{meas}(t_n) - G_{meas}(t_0))$$

Let:

$$f_1 = G(t)\frac{Q(t)}{1+\alpha_G Q(t)}$$

$$f_2 = \int_{t_0}^{t_n} -p_G G(t) + \frac{P(t)+EGP-CNS}{V_G}\ dt - (G_{meas}(t_n) - G_{meas}(t_0))$$

The equation becomes:

$$\int_{t_0}^{t_n} S_I(t) \times f_1\ dt = f_2 \tag{4.2}$$

In this study, $S_I(t)$ is identified as the linear combination of BFs, $\Phi_i(t)$, defined:

$$\begin{bmatrix} \Phi_1(t) & \Phi_2(t) & \cdots & \Phi_n(t) \end{bmatrix} \begin{bmatrix} \gamma_1 \\ \gamma_2 \\ \vdots \\ \gamma_n \end{bmatrix} = S_I(t) \tag{4.3}$$

Combining Eqs. (4.2) and (4.3), the BF coefficients, $\gamma_i$, can be solved for using least squares. Overall, minimizing the error between $f_1$ and $f_2$, and thus, the modelled $G(t)$ and clinically measured BG, given the clinical interventions:

$$\begin{bmatrix} \int_{t_0}^{t_n} \Phi_1(t) \times f_1 \, dt & \int_{t_0}^{t_n} \Phi_2(t) \times f_1 \, dt & \cdots & \int_{t_0}^{t_n} \Phi_n(t) \times f_1 \, dt \end{bmatrix} \begin{bmatrix} \gamma_1 \\ \gamma_2 \\ \vdots \\ \gamma_n \end{bmatrix} = f_2 \tag{4.4}$$

Where: $\gamma_i$ = basis function fitted coefficient i

The modelled BG solution, $G(t)$, can then be simulated using the ICING model, Equations (1.1) to (1.7), with the identified $S_I(t)$ trace and same clinical interventions. The resultant simulated BG trace can be used for assessment of model fit. Depending on the shape of the chosen BF, the dynamics of the identified $S_I$ trace are restricted accordingly. As a result, the modelled BG, $G(t)$, goodness-of-fit to the clinical BG data is a function of BF shape.

Given the nature of $S_I$ within the ICING model, a minimum of 2 BG measurements per BF (1 Change in BG per equation) are required to identify each BF. A new BF occurs every KW. Therefore, to ensure identifiability, 2 BG measurements per KW are needed. As the measurement intervals offered by STAR are 1-3 hours [128], [147], a KW greater than or equal to 180 minutes (3 hours) is required

to ensure BF identifiability without having to assume intermediate BG measurements, as is done currently with the 60 minute KW zeroth order B-spline BFs.

### 4.2.2 Physiological Representation

In non-critically ill patients, under steady state conditions, $S_I$ is considered to be relatively constant [252], [253]. However, within critically ill patients the stress-heightened state and/or the drugs given after insult can result in a highly dynamic counter-regulatory hormone and cytokine response, inducing frequent changes in BG [236]–[238], [240] and thus effective $S_I$ [31], [112], [145], [228], [254], [255]. In addition, $S_I$ is generally considered to occur in a continuous manner as it is a physiological signal. Thus, a 2nd order B-spline BF is chosen to represent $S_I$ as a smooth continuous trace.

### 4.2.3 Basis Functions

#### *4.2.3.1 B-spline BFs*

B-spline BF are defined by the equations below [222]:

When k = 0:
$$\Phi_i(t) = \begin{cases} 1 & t_i \leq t < t_{i+1} \\ 0 & Otherwise \end{cases} \tag{4.5}$$

When k > 0:
$$\Phi_{i,k}(t) = \frac{t - t_i}{t_{i+k} - t_i}\Phi_{i,k-1}(t) + \frac{t_{i+k} - t}{t_{i+k} - t_i}\Phi_{i+1,k-1}(t) \tag{4.6}$$

Where: $\Phi$ = basis function, $k$ = basis function order, $i$ = basis function # $t_i$ = knot-width location

The range of $t_i \leq t < t_{i+1}$ defines the KW of the given BF.

#### *4.2.3.2 Zeroth order B-spline BFs (Current Technique)*

Zeroth order B-spline BFs are based on the piece-wise function defined in Eq. (4.5). When $k = 0$ the equation becomes:

$$\Phi_i(t) = \begin{cases} 1 & KW \times (i-1) < t < KW \times (i) \\ 0 & Otherwise \end{cases} \tag{4.7}$$

Where: $\Phi_i$ = basis function i, $KW$ = knot width, $i$ = basis function #

This BF holds a constant value over the period of the KW. The current BF used to fit the ICING model uses a 60 minute KW, zeroth order B-spline BF [153], as shown in Fig. 4.1. It thus requires interpolated measurements every 60 minutes between any more widely spread clinical BG measurements.

#### *4.2.3.3 2nd order B-spline BFs*

2nd order B-spline BFs are based on the piece-wise function defined in Eq. (4.5). When $k = 2$ the equation becomes:

$$\Phi_i(t) = \begin{cases} \frac{(t-KW\times i)^2}{2\times KW^2} & KW \times i < t < KW \times (i+1) \\ \frac{-1}{KW^2}(KW \times (i+\frac{3}{2}) - t)^2 + \frac{3}{4} & KW \times (i+1) < t < KW \times (i+2) \\ \frac{(KW\times(i+3)-t)^2}{2\times KW^2} & KW \times (i+2) < t < KW \times (i+3) \\ 0 & Otherwise \end{cases} \tag{4.8}$$

$$\sum_{i=1}^{n} \Phi_i(t) = 1 \ \forall t \tag{4.9}$$

Where: $\Phi_i$ = basis function i, $KW$ = knot width, $i$ = basis function #,

$n$ = number of basis functions

In contrast to Eq. (4.7), these BFs overlap each other, as shown in Fig. 4.1. The inherent properties of B-spline BFs in Eq. (4.9) ensure no assumed or underlying waveform is induced into the identified solution, and a constant value can also be represented.

A smooth 2nd order polynomial BF ensures continuous differentiability of two orders. Physiologically, $S_I$ thus varies smoothly and continually. Equally, the first derivative of $S_I$ may provide significant physiological insight not currently available using non-differentiable, discontinuous zeroth order BFs.

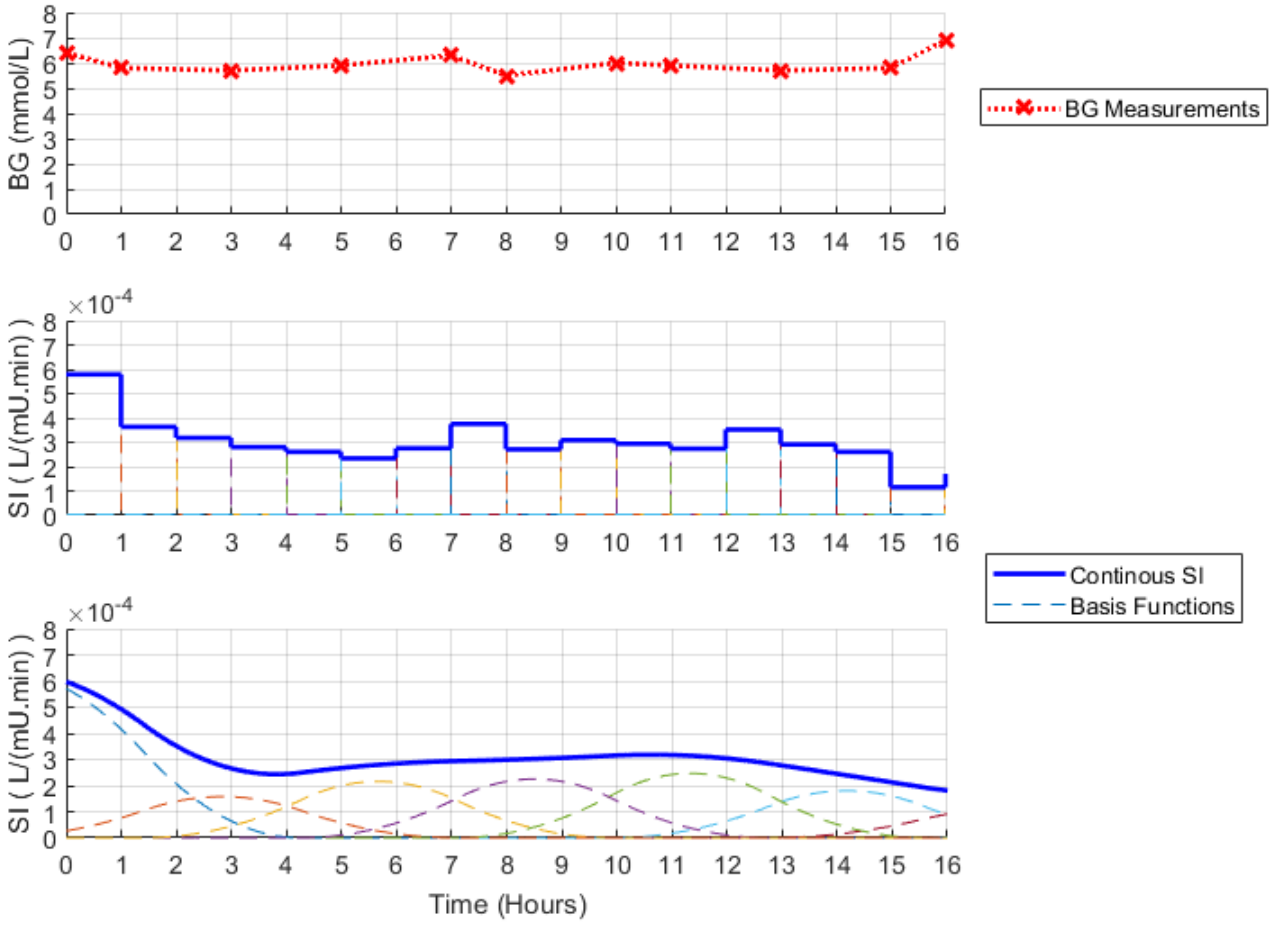



Figure 4.1: Comparison of the basis function (BF) being investigated. (Top) BG measurement data used to identify insulin sensitivity ($S_I$). (Middle) Zeroth order 60 minute knot-width (KW) B-spline BFs, current fitting technique. (Bottom) 2nd order 170 minute KW B-spline BFs.

### 4.2.4 Clinical data

Clinical data for validation analysis was obtained from a published 20 patient benchmark cohort [101] and a 72 patient sub-cohort of the STAR cohort [215]. The cohorts were specifically chosen for validation analysis as they used glucometers of considerably different precision. STAR patients were selected if they started GC after 2014, ensuring they were using a different, lower error, glucometer to that used in the benchmark cohort. The Upper South Regional Ethics Committee, New Zealand granted ethics approval for the audit, analysis, and publication of these data. Each cohorts clinical GC performance results are presented in Table 4.1 for reference.

Table 4.1: Clinical GC performance statistics of the benchmark and STAR sub-cohort.

| | Benchmark cohort | STAR sub-cohort |
|---|---|---|
| Num Patients | 20 | 72 |
| Total hours | 6918 | 6386 |
| Num BG measurements: | 4482 | 3089 |
| Measures/day (Per-Patient) | 15.4 [13.5 - 17.3] | 11.5 [10.6 - 13.7] |
| BG median (mmol/L) | 5.7 [5.3 - 6.0] | 6.6 [6.3 - 7.1] |
| BG mean (mmol/L) | 5.9 [5.5 - 6.2] | 6.7 [6.5 - 7.2] |
| BG SD (mmol/L) | 0.9 [0.8 - 1.3] | 1.0 [0.8 - 1.4] |
| % BG <2.22 mmol/L | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] |
| % BG <4.4 mmol/L | 5.2 [2.4 - 10.0] | 0.0 [0.0 - 0.0] |
| % BG within 4.0-8.0 mmol/L | 95.1 [90.2 - 97.7] | 90.1 [78.4 - 93.9] |
| % BG >10.0 mmol/L | 0.0 [0.0 - 0.6] | 0.7 [0.0 - 4.1] |

*blood glucose (BG), standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

### 4.2.5 Basis Function Fit Analysis

Zeroth order B-spline BFs (KW = 60) are compared to 2nd order B-spline BFs in terms of fit and susceptibility to noise. Four 2nd order B-spline BF KWs are assessed, ranging from 180 to 300 minutes. The most appropriate KW will be determined by which BF best represents the $S_I$ dynamics.

#### *4.2.5.1 Fit Assessment*

In all modelled systems there are both modelling and measurement errors, both contributing to the overall fitting error. If a model is *'over fit'* to measured data there is low overall fitting error, as the identified model dynamics also capture measurement error. However, in a *'good fit'* to measured data, measurement error is still observed in the overall fitting error.

As identified $S_I$ dynamics depend on the BF used to represent it, the resulting ICING model fitting error is also a function of the BF used. Therefore, modelling error can be minimized by choosing an appropriate BF. However, to avoid over fitting, the overall fitting error should not be less than the expected measurement error of the BG meter used, indicating minimal model error without *'over fitting'*.

The overall fitting error (Goodness-of-fit) of each of the BFs is assessed by the relative difference between the resultant model BG solution and clinical BG measurements, on both the benchmark

cohort and STAR sub-cohort. The relative difference error distribution characteristics are compared to error metrics for the point of care (PoC) measurement device used with each cohort. The benchmark cohort used the Arkray Super-Glucocard$^{TM}$ II glucometer (Arkray, Minnesota, USA). However, independent published glucometer error data for the Arkray Super-Glucocard$^{TM}$ II could not be found, so the similar Glucocard X Meter (Arkray, Inc., Kyoto, Japan) published in [256], [257] is used (Mean = 0%, SD = 9.35%). The STAR cohort used the Roche Accu-Chek Inform II (F. Hoffmann-La Roche Ltd, Basel, Switzerland), with glucometer error metrics in [258], [259] (Mean = 0%, SD = 6.0%).

#### *4.2.5.2 Sensitivity to added erroneous BG measurements*

To further illustrate the reduction in *'over fitting'*, or susceptibility of the BF to measurement noise, the current zeroth order B-spline BF and best 2nd order B-spline BF are used to identify the $S_I$ trace on 2 patients in which erroneous BG measurements are added. The erroneous BG measurements are added in addition to the *'real'* clinical BG measurements and put at extremely unlikely levels relative to the clinical BG data based on what is seen clinically. The identified $S_I$ trace and resulting modelled BG of the two different BFs are compared in terms of susceptibility to the added erroneous BG measurements.

To work out the maximum expected change in BG, the initial BG and proceeding change in BG, over an hour, was used to form a stochastic model. From this stochastic model the most likely change above and below the current can be determined. Data from 221 patients treated with the STAR protocol in Christchurch Hospital ICU, NZ was used to create the stochastic model seen in Fig. 4.2.

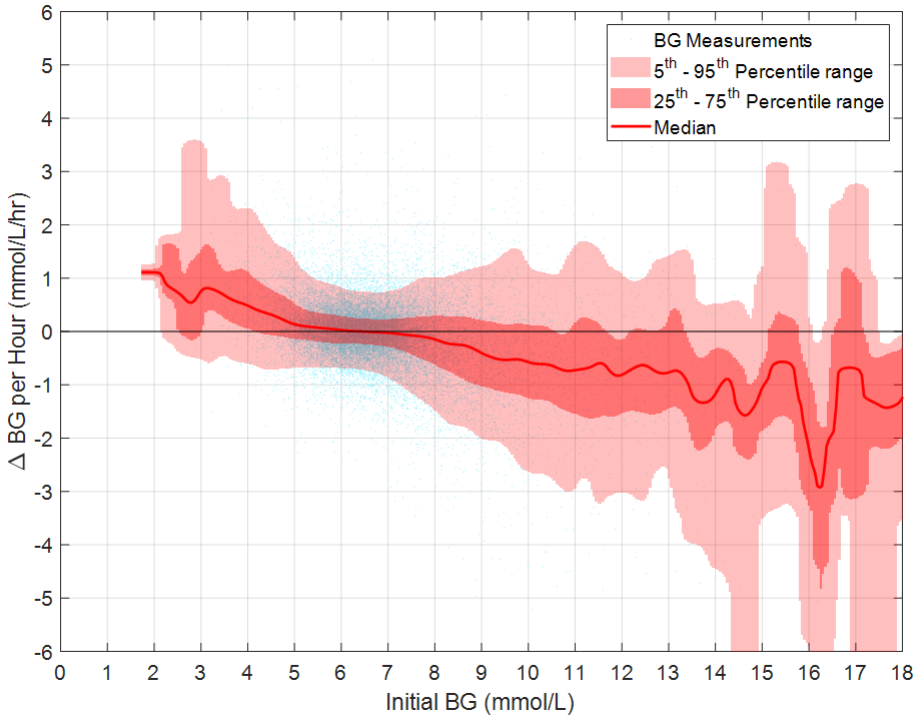



Figure 4.2: Stochastic model of hourly changes in blood glucose (BG) given the initial BG level, based on data from the STAR Christchurch Hospital, New Zealand (NZ) cohort.

From Fig. 4.2 it can be seen that a change in BG of 2.0 mmol/(L.hr) is very unlikely at all BG levels, especially below 10.0 mmol/L. Above 13 mmol/L and below 3.5 mmol/L the bounds are very wide due to low numbers of measurements in this region, Table 4.1. Therefore, the erroneous BG measurements are added with BG changes greater than 2.0 mmol/(L.hr).

## 4.3 Results

### 4.3.1 Physiological Representation

The 2nd order B-spline BF is shown to have a considerably more physiologically representative signal compared to the current zeroth order B-spline BF technique, Fig. 4.3 and Fig. 4.4. This interpretation is especially apparent around hour 30 in Fig. 4.3 and hour 6 in Fig. 4.4, where the 2nd order B-spline BF provides a smooth solution to $S_I$ without the excessive variation seen in the zeroth order B-spline BF. In general, the 2nd order B-spline BF provides a very plausible solution to the patient-specific time varying $S_I$.

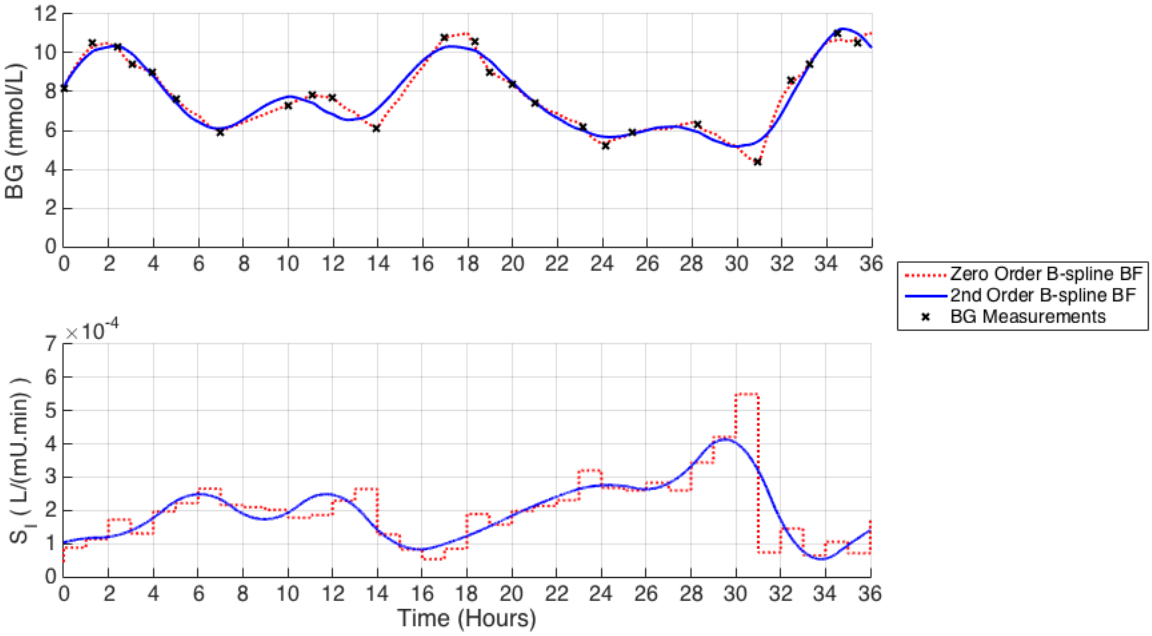



Figure 4.3: Example patient 1. Comparison of the physiological representation for current zeroth order 60 minute knot-width (KW) B-spline basis function (BF), and the 2nd order 180 minute KW B-spline BF. Top Panel: Measured BG and the resulting modelled $G(t)$. Bottom Panel: insulin sensitivity ($S_I$) representation over time.

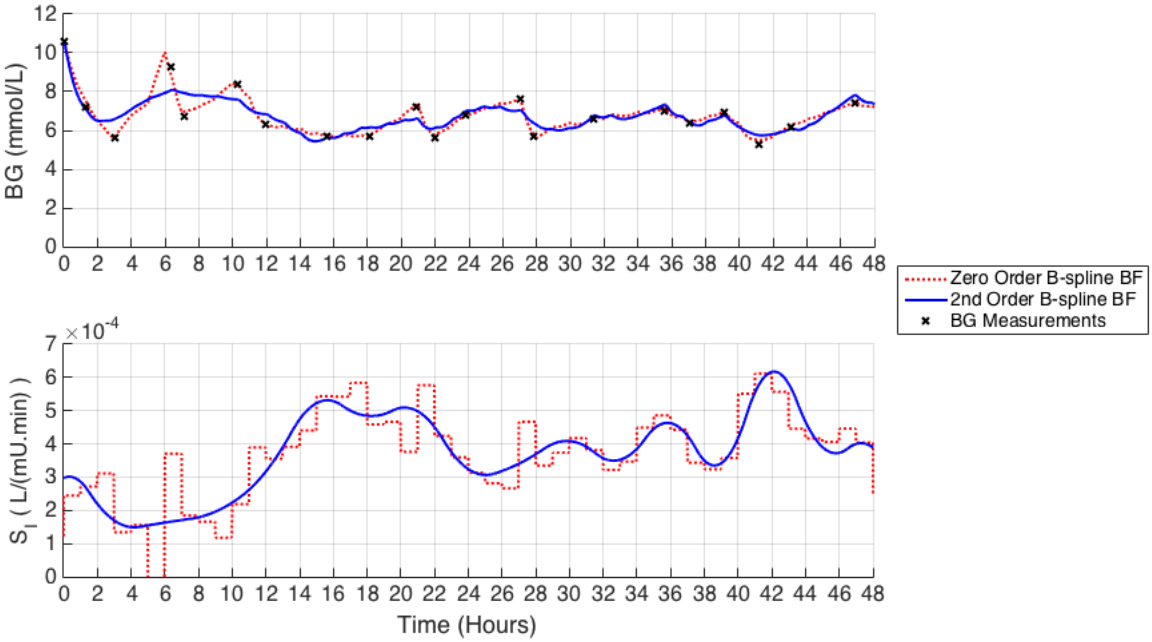



Figure 4.4: Example patient 2. Comparison of the physiological representation for current zeroth order 60 minute knot-width (KW) B-spline basis function (BF), and the 2nd order 180 minute KW B-spline BF. Top Panel: Measured BG and the resulting modelled $G(t)$. Bottom Panel: insulin sensitivity ($S_I$) representation over time.

### 4.3.2 Basis Function Fit Analysis

#### *4.3.2.1 Fit Assessment*

Tables 4.2 and 4.3 show the relative fitting error characteristics and expected error of the glucometers used for the benchmark cohort and STAR sub-cohort, respectively, for each BF considered. The zeroth order B-spline BF has considerably less fitting error, in both cohorts than what would be expected from the BG meter. In contrast, all of the 2nd order B-spline BFs have an error approximately equal to or greater than what would be expected from the relevant BG meter, increasing with KW. In addition, the relative fitting error decreases between the benchmark cohort and STAR sub-cohort, as the sensor precision improves, as would be expected, but only for the 2nd order B-spline BFs. Overall, the 180 minute KW BF gives the closest fitting error to the BG meter used in both cohorts.

Table 4.2: Characteristics of the relative fitting error of the various basis function (BF) being investigated on the benchmark cohort.

| B-spline BF | Zeroth order B-spline | 2nd order B-spline | | | PoC BG Meter [256], [257] |
|---|---|---|---|---|---|
| Knot Width (KW) | 60 | 180 | 240 | 300 | - |
| Mean Rel. BG Error (%) | 0.7 | 1.2 | 1.4 | 1.6 | **0** |
| SD Rel. BG Error (%) | 1.0 | 8.7 | 10.0 | 11.0 | **9.35** |

*blood glucose (BG), standard deviation (SD), point of care (PoC).

Table 4.3: Characteristics of the relative fitting error of the various basis function (BF) being investigated on the STAR sub-cohort.

| B-spline BF | Zeroth order B-spline | 2nd order B-spline | | | PoC BG Meter [258], [259] |
|---|---|---|---|---|---|
| Knot Width (KW) | 60 | 180 | 240 | 300 | - |
| Mean Rel. BG Error (%) | 0.7 | 1.2 | 1.3 | 1.3 | **0** |
| SD Rel. BG Error (%) | 2.4 | 6.0 | 7.4 | 8.2 | **6.0** |

*blood glucose (BG), standard deviation (SD), point of care (PoC).

#### *4.3.2.2 Sensitivity to added erroneous BG measurements*

The current zeroth order B-spline BF and the 180 minute KW 2nd order B-spline BF are identified on two patients in which highly erroneous and very unlikely erroneous BG measurements are introduced to test robustness to error. Note, these patients are different from the patients used in Fig. 4.3 and Fig. 4.4. The difference in the identified $S_I$ trace and resulting modelled BG of the Zeroth order B-spline BF solution can be directly compared in Fig. 4.5 and Fig. 4.6. The 2nd order B-spline BF solution is smoother and less sensitive to the erroneous measures, where the zeroth order B-spline BF over fits the erroneous measures via physiologically unrealistic changes in $S_I$.

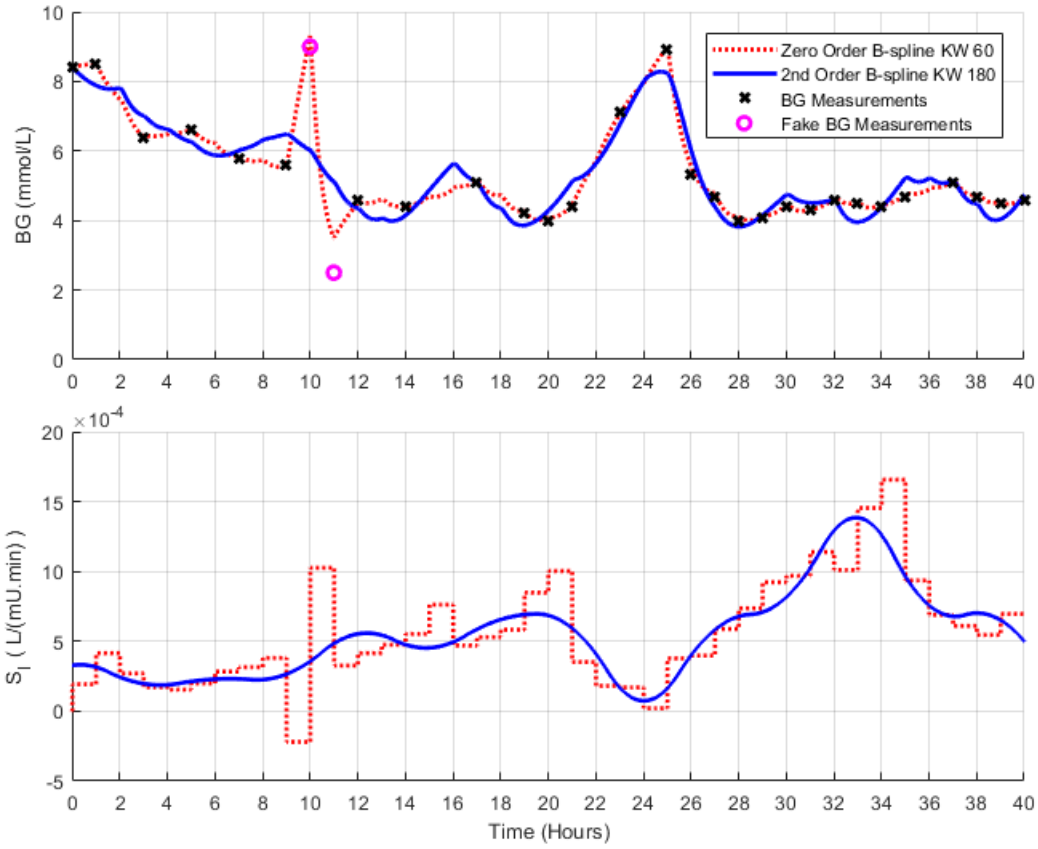



Figure 4.5: erroneous blood glucose (BG) measurement example 1. Comparing the influence of erroneous BG measurements on the identified BG and insulin sensitivity ($S_I$) solution for the current zeroth order B-spline (knot-width (KW)=60) and 2nd order B-spline (KW=180) basis function (BF). Top Panel: Measured BG and the resulting modelled $G(t)$. Bottom Panel: insulin sensitivity ($S_I$) representation over time.

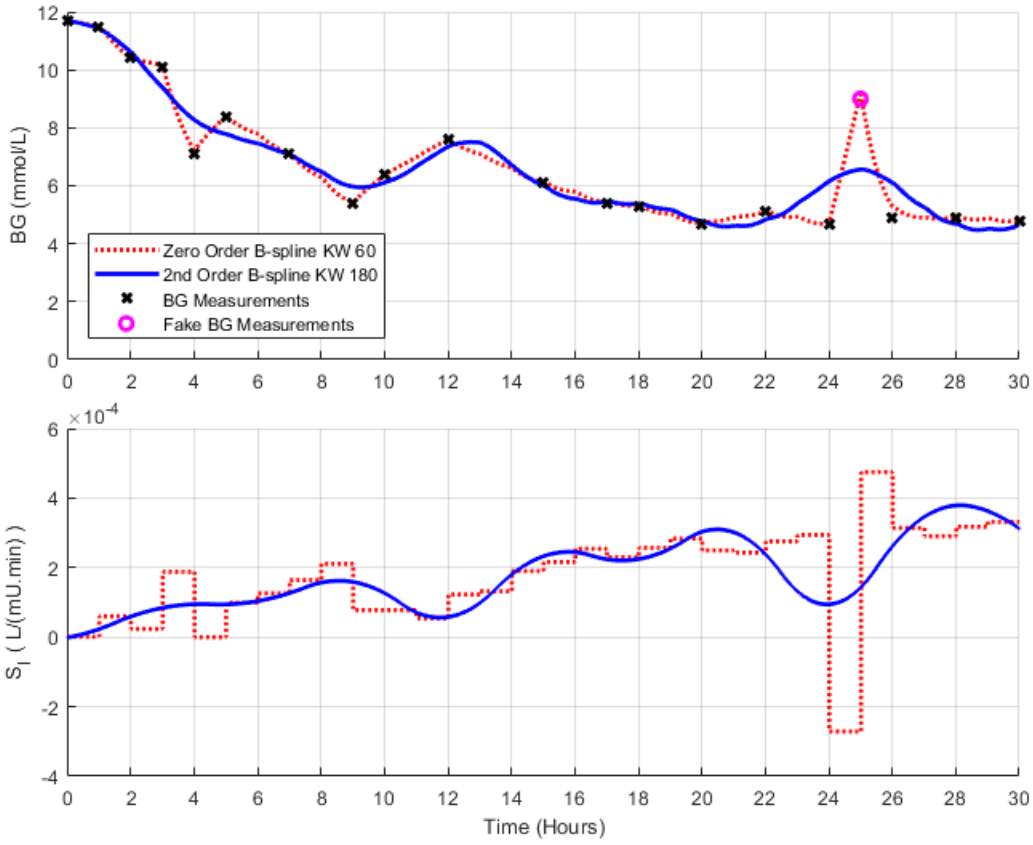



Figure 4.6: erroneous blood glucose (BG) measurement example 2. Comparing the influence of erroneous BG measurements on the identified BG and insulin sensitivity ($S_I$) solution for the current zeroth order B-spline (knot-width (KW)=60) and 2nd order B-spline (KW=180) basis function (BF). Top Panel: Measured BG and the resulting modelled $G(t)$. Bottom Panel: insulin sensitivity ($S_I$) representation over time.

## 4.4 Discussion

### 4.4.1 Physiological Representation and Identifiability

Representing $S_I$ with a smooth continuous 2nd order B-spline BF results in a considerably more realistic identified $S_I$ trace, as very few things in reality are truly represented by a piece-wise constant, non-continuous signal. As seen in Figs. 4.3 and 4.4, the previous BF discrete step wise jumps in $S_I$ are now represented as smooth gradual changes. The 2nd order B-spline BF behaves like a low pass filter, reducing the effects of rapid changes in BG, and taking a mean value approximation to high frequency BG changes. This behaviour is especially prominent in the first 10 hours of Fig. 4.4. In addition, the 180 minute KW of the 2nd order B-spline BF requires no assumed intermediate BG measurements to identify $S_I$. Therefore, the modelled BG trace will be more model dependent, less sensitive to errors, and thus more physiologically representative of the measured data and clinical inputs.

### 4.4.2 Basis Function Fit Analysis

#### *4.4.2.1 Fit Assessment*

The relative fitting error of the 2nd order B-spline BFs decreased as KW decreased, as seen in Tables 4.2 and 4.3. For both the benchmark cohort and STAR sub-cohort, only the 2nd order B-spline BFs provided a *'realistic'* fitting error variance approximately equal to that of the BG meter (benchmark cohort: 8.7-11.0% vs. 9.35% [256], [257], Table 4.2 and STAR sub-cohort: 6.0-8.2% vs. 6.0% [258], [259], Table 4.3). In contrast, in both cohorts, the zeroth order B-spline BF had considerably less fitting error variance than the BG meter (Benchmark 1.0% vs. 9.35%, Table 4.2 and STAR sub-cohort 2.4% vs. 6.0%, Table 4.3). This latter result suggests the identified current BF $S_I$, and resultant BG trace may be *'over fitted'* to the clinical BG measurements. As a result, physiological changes in $S_I$ occurring from treatment may be swamped by rapid changes in $S_I$ driven by BG measurement errors, as well-illustrated in Figs. 4.5 and 4.6.

The relative fitting error shown by the 180 minute KW 2nd order B-spline BF provided the most plausible solution having a variance very similar to that expected from the BG meter used in each

cohort. In addition, the 180 minute KW 2nd order B-spline BFs decreased fitting error variance when BG meter precision improved (8.7% -> 6.0%, Tables 4.2 and 4.3), where the current zeroth order B-spline BF increased (1.0 -> 2.4%,Tables 4.2 and 4.3). Overall, these results show the 180 minute KW 2nd order B-spline BF results in a much more *'realistic'* modelled BG fit to the clinical BG measurements than the current BF technique.

#### *4.4.2.2 Sensitivity to added erroneous BG measurements*

The 180 minute KW 2nd order B-spline BF was considerably less influenced by erroneous or highly erroneous BG measurements than the current zeroth order B-spline BF, as seen in Figs. 4.5 and 4.6. This outcome is again due to the 2nd order B-spline BF being essentially a low-pass filter, reducing the effect of any rapid changes in BG, and effectively taking a moving average of the BG data, reducing the effect of individual outliers. It is important to note the 2nd order B-spline BFs can still accommodate the vast majority of physiologically rapid changes in BG seen in Fig. 4.2. However, the clinical erroneous measurements that occur well outside these bounds are ignored. Thus, this choice of BF reduces the impact of outliers without imposing restrictions on large, physiologically realistic responses.

As the introduced 180 minute KW continuous 2nd order B-spline BF has more restricted $S_I$ dynamics, some of the outlying hour-to-hour changes used in the stochastic model [145], as seen in Chapter 3 *Evaluation and simplification of STAR's stochastic model*, of the STAR GC algorithm [128], [147] will be significantly reduced. As a result, significant treatment changes, offered previously in response to a large step change in $S_I$, will now be reduced in numbers, as STAR doses insulin on risk using these stochastic models [128], [147], [149].. For example, at hour 25 of Fig. 4.6 the erroneous BG measurement results in a very low $S_I$ value. Due to the newly measured BG being out of the 4.4-8.0 mmol/L targeted band STAR would raise insulin to try and rapidly lower their BG. However, as this measurement is erroneous, the calculated $S_I$ is much lower than what they are likely to be at. As a result, the patient's risk of hypoglycaemia is increased. Therefore, as the $S_I$ changes are less prone to erroneous measurements and more restricted, STAR's GC patient safety and effectiveness should be improved.

Overall, the 180 minute KW continuous 2nd order B-spline BFs allow more information to be captured about patient-specific $S_I$ dynamics. Thus, many new continuous time analyses could be undertaken, such as frequency analyses, and analysing the 1st and 2nd derivative of $S_I$ for clinical information on its rate of change. These characteristics have already been shown to be related to physiologically observed events, such as the onset of sepsis and cardiac events, which each induce rapid $S_I$ changes [220] and could be more easily detected or diagnosed with this rate of change information. None of these capabilities or potential capabilities are available form any model used today. Future work in these areas provides promising potential improvements for GC. In addition, as rapid changes in BG can now not be captured by rapid $S_I$ changes, areas of improvement in ICING model are more apparent, and thus can be specifically addressed.

Before this technique of $S_I$ fitting can employed directly into a GC algorithm such as STAR several areas need to be addressed. Currently, the BF coefficients are identified by assessing the entire patient's data set. However, in the clinical setting the BF coefficients will only be able to be identified up to the current BG measurement. Therefore, when a new BG measurement is taken, and $S_I$ identified, the previously identified BF coefficients, and, as a result, $S_I$ trace may change to better fit the new BG measurement. As the previous $S_I$ value may change in the process of getting the current $S_I$ value, the current stochastic prediction method used by STAR, predicting future $S_I$ based on current $S_I$, is not possible. Therefore, before this technique can be used for stochastic prediction of future $S_I$ a better understanding of the variability in $S_I$ value, before and after a BG measurement is added, needs to be assessed.

## 4.5 Summary

This chapter investigated 2nd order B-spline BFs as an alternative to the current non-physiologically representative zeroth order B-spline (KW = 60) BFs, used for $S_I$ identification in the ICING model. Various KW 2nd order B-spline BFs were investigated and compared to the current zeroth order B-spline BF. The BFs were compared in terms physiological relevance, identifiability, robustness to erroneous measurements, and susceptibility to noise. 2nd order B-spline BFs were shown to result in a considerably more physiologically representative $S_I$ trace. The 180 minute KW 2nd order B-spline BF provided the most physiologically realistic fit to the BG measurements, in both the benchmark cohort and STAR sub-cohort, having very similar fitting error variances to that of the respective BG meter used, whilst showing significantly less susceptibility to erroneous BG measurements.

Overall, the 180 minute KW 2nd order B-spline BFs results in a more physiologically representative, identifiable $S_I$ and a more realistic resulting BG solution. In addition, the smooth and continuous characteristic of the 2nd order B-spline BF opens up several new potential continuous time analyses of metabolic dynamics, and allows areas for improvements in modelling to be more easily identified. However, the ability for this technique to be directly employed in GC needs further investigation before direct use in the clinical setting.

# Part II:

# Assessment of the Stochastic TARgeted model-based glycaemic controller

> It is a mistake to think you can solve any major problems just with potatoes.
>
> Douglas Adams

# Chapter 5

# Clinical performance review of the STAR Glycaemic Control protocol

## 5.1 Background

There is currently much debate about whether or not GC is beneficial for an ICU patient, with several studies showing evidence both for [29], [30], [51], [101], [102] and against [103], [109], [112]–[117] its use. However, the ability to provide safe, effective control across patients and clinical practices is a necessary requirement before being able to assess the impact of GC on clinical outcomes [260]. Safe and effective GC is an area many of these studies have failed to address [103], [105], [107], [108], [110], [111], [213], and, as a result, have significantly increased the risk of hypoglycaemia (6.8% - 29% of patients experienced BG $< 2.2$ mmol/L), which is associated with increased mortality [34]–[36], [261]. Hindering the ability to observe any benefits of GC.

The stress response a critically ill patient experiences is highly complex, variable, and dynamic [122], making safe, effective control of BG difficult. In particular, large changes in a patient's $S_I$ over short periods of time [122], [123], [254], particularly in the first 48 hours [262] where hypoglycaemia has a

[1] **K. W. Stewart**, C. G. Pretty, H. Tomlinson, F. L. Thomas, J. Homlok, S. N. Noémi, A. Illyés, G. M. Shaw, B. Benyó, and J. G. Chase, "Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis," Ann. Intensive Care, vol. 6, no. 1, p. 24, 2016.

[2] **K. Stewart**, C. G. Pretty, F. Thomas, G. M. Shaw, T. Desaive, B. Benyo, J. Homlok, A. Illyes, N. S. Nemedi, and J. G. Chase, "Generalizability of a Nonlinear Model-based Glycemic Controller," in 4th IFAC International Conference on Intelligent Control and Automation Sciences (ICONS), 2016, vol. 49, no. 5, pp. 212–217.

stronger association to mortality [34], make achieving safe GC difficult. Therefore, a patient-specific approach which accounts for this variability is needed.

In general, previous studies failed to achieve safe consistent GC due to the GC protocols not being able to observe or identify individual patient-specific dynamics, and instead providing GC based on an absolute or change in BG value, without reference to the causative treatment. These protocols also often lack knowledge of nutrition inputs to place the measured BG value in context. Thus, a more patient-specific approach to GC is needed to successfully manage such significant inter- and intra- patient variability [123], [124].

The STAR GC protocol appeared the most promising of the ICU GC protocols reviewed in Section 1.2.3 *Glycaemic Control Protocols*. However, the reviewed results were based on a clinical pilot trial (N=10) [128]. Since this pilot trial STAR has been the standard of care in Christchurch Hospital ICU, Christchurch, NZ and in the Kálmán Pándy Hospital ICU, Gyula, Hungary from 2011 to present (N = approximately 800). Therefore, a deeper investigation into the STAR GC performance is required to confirm the preliminary results of clinical pilot trial. Note the predecessor of STAR in Christchurch was the paper-based, model-derived [152], SPRINT GC protocol [31], [101], which is used for comparison in this analysis, as it achieved tight GC while reducing hypoglycaemia, and also morbidity and mortality [142], [143].

This chapter provides a dual-centre retrospective analysis of the STAR GC protocol, demonstrating that patient-specific, safe, effective GC is possible with the STAR protocol and that it is also generalizable across/over different units and clinical practices. From this review future areas of development for the STAR GC protocol will be able to be identified.

## 5.2 Methods

### 5.2.1 Comparisons

This dual-centre retrospective analysis provides 2 comparisons to assess:

1. Performance and Safety: STAR is compared to SPRINT in Christchurch to provide a comparison between patient protocols in the same unit and clinical practice, and demonstrate equivalent or better performance and safety of STAR to a successful protocol [101].
2. Generalizability: STAR Christchurch is compared to STAR Gyula to test generalizability of safety and performance over significantly different clinical practice cultures and approaches. Repeatability across clinical practices is a necessity for widespread uptake and achieving the benefits of GC [260].

The metrics compared are:

- Performance: Percentage of time in BG band (4.4-8.0 mmol/L) [61].
- Safety: Number of severe hypoglycaemic cases (BG $<$ 2.2 mmol/L) [35].
- Safety: Number of moderate hypoglycaemic cases (BG $<$ 4.0 mmol/L) [34].

### 5.2.2 Patients

#### *5.2.2.1 Cohorts*

This study compares clinical data from 3 cohorts:

**I** Patients treated using STAR in Christchurch Hospital ICU, Christchurch, NZ, from June 2011 – May 2015.

**II** Patients treated using STAR in Kálmán Pándy Hospital ICU, Gyula, Hungary, from December 2011 – May 2015.

**III** Patients treated using SPRINT in Christchurch Hospital ICU, Christchurch, NZ, from July 2005 – May 2007.

Patients in these 3 cohorts exclude those who spent less than 10 hours on protocol, and were fed on average greater than 120% of their Society of Critical Care Medicine (SCCM)/ACCP caloric target

[156]. Patients who spent less than 10 hours on protocol were excluded as they were considered to not have a significant amount of time on protocol to fairly assess the performance or be clinically affected by good GC. Patients who were fed greater than 120% of their calorific target were excluded as this nutrition level is well outside the recommendations of STAR and SPRINT, as well as well-accepted clinical, guidelines [156] and typical practice [263]. The number of patient episodes excluded due to each of these filtering criteria can be seen in Table 5.1.

STAR also allows a different target band to be specified in some clinical cases. For this analysis the most common target (The default 4.4-8.0 mmol/L target) in both Christchurch and Gyula was chosen so the largest number of patients were available to compare the *'matched treatment options'*. Therefore, patients on the STAR protocol who did not target the 4.4-8.0 mmol/L BG band were excluded. These were commonly diabetic patients who were treated with a 5.0-10.0 mmol/L target BG band to minimise the effect of relative hypoglycaemia [264]. Thus, all STAR patients compared used the STAR framework in the same manner with respect to BG and nutrition targets. It should be noted that all SPRINT patients targeted the 4.0-6.1 mmol/L BG band as the SPRINT protocol was not flexible to different targets [265].

Table 5.1: Episode filtering statistics.

| Number of episodes (%) | SPRINT Christchurch | STAR Christchurch | STAR Gyula |
|---|---|---|---|
| Initial Number | 487 | 625 | 68 |
| Different GC target to protocol | 0 (0.0%) | 225 (36.0%) | 11 (16.2%) |
| Episode length $<$ 10 hours | 58 (11.9%) | 49 (7.8%) | 6 (8.8%) |
| Fed over 120% Target | 74 (15.2%) | 15 (2.4%) | 4 (5.9%) |
| Remaining for analysis | 355 (72.9%) | 336 (53.8%) | 47 (69.1%) |

Demographic data for these cohorts are presented in Tables 5.2 and 5.3, aligned with the two main comparisons. Some data is unavailable for the STAR Gyula cohort in Table 5.3 due to differences in the typical data collected. The missing data does not impact the assessment of generalizability of the safety and performance of STAR.

Table 5.2: Patient Demographics for the STAR and SPRINT Christchurch cohorts.

| Cohort Characteristics | SPRINT Christchurch | STAR Christchurch | P-Value |
|---|---|---|---|
| Total patients | 292 | 267 | |
| Age | 63 [48 : 73] | 65 [55 : 72] | 0.28 |
| Percent male | 62.7 | 65.5 | 0.48 |
| Length of ICU Stay (Days) | 6.2 [2.7 : 13.0] | 5.7 [2.5 : 13.4] | 0.7 |
| % Operative | 38.7 | 34.8 | 0.38 |
| APACHE II Score | 19.0 [15.0 : 24.5] | 21.0 [16.0 : 25] | 0.05 |
| APACHE II RoD (%) | 29.0 [16.0 : 51.0] | 33.0 [15.0 : 53.0] | 0.41 |
| ICU Mortality (%) | 18.2 | 24.3 | 0.08 |
| Hospital Mortality (%) | 26 | 30 | 0.35 |
| Hospital SMR | 0.76 | 0.86 | - |
| Mortality on GC Protocol (%) | 5.5 | 6.4 | 0.72 |

*Intensive Care Unit (ICU), Acute Physiology And Chronic Health Evaluation (APACHE), standardized mortality ratio (SMR), Risk of Death (RoD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

Table 5.3: Patient Demographics for the STAR Christchurch and Gyula cohorts.

| Cohort Characteristics | STAR Gyula | STAR Christchurch | P-Value |
|---|---|---|---|
| Total patients | 47 | 267 | |
| Age | 66 [58 : 71] | 65 [55 : 72] | 0.72 |
| Percent male | 61.7 | 65.5 | 0.62 |
| Length of ICU Stay (Days) | 14.0 [8.0 : 20.5] | 5.7 [2.5 : 13.4] | <0.001 |
| APACHE II Score | 32.0 [28.0 : 36.0] | 21.0 [16.0 : 25] | <0.001 |
| ICU Mortality (%) | 38.3 | 24.3 | 0.05 |
| Mortality on GC Protocol (%) | 0 | 6.4 | 0.09 |

*Intensive Care Unit (ICU), Acute Physiology And Chronic Health Evaluation (APACHE). Data presented in Median [inter-quartile range (IQR)] where appropriate.

#### *5.2.2.2 Ethics, consent and permissions*

The Upper South Regional Ethics Committee, NZ granted approval for the retrospective audit, analysis and publication of the Christchurch patient data. According to the local ethical codes in Hungary, the retrospective study of the Gyula cohort was considered a clinical data audit, and only required depersonalization of data without the need for individual patient consent to analyse or publish the anonymized data.

#### *5.2.2.3 Episodes of GC*

As a single patient may be treated by a protocol on several distinct occasions separated by significant breaks. Therefore, a distinction is made between a patient and an episode of GC. A patient is considered to be a person with the same ICU admission number, and an episode is considered to be a period of contiguous treatment by GC. Therefore, there can be multiple episodes per patient.

An episode was defined as a period of GC (10 hours or more) in which there are no breaks in BG measurements longer than 5 hours. If a gap in data exceeded 5 hours, it was considered that GC had been stopped and restarted. Considering the maximum measurement interval on STAR is 3 hours, this choice accounts for reasonable variance in measurement intervals.

### 5.2.3 Clinical Practices and Implementation

#### *5.2.3.1 Christchurch Hospital ICU, New Zealand*

STAR has been the standard of care in the Christchurch Hospital ICU since June 2011. This facility is a mixed medical, tertiary affiliated ICU. Starting criteria for STAR in Christchurch is two successive BG measurements over 8 mmol/L within a 4-hour period. intravenous (IV) insulin is delivered in hourly bolus form, with added background infusions of up to 3U/hour when insulin requirements are high and sustained [128], [147]. Blood for BG measurement was typically taken directly from an arterial line, and measured using an Arkray Super Glucocard$^{TM}$ II glucometer (Arkray, Minnesota, USA), (2011-2012) or a Roche Accu-Chek Inform II (F. Hoffmann-La Roche Ltd, Basel, Switzerland), (2012-2015).

SPRINT, the predecessor to STAR, used the same entry criteria as STAR and used the same insulin delivery procedures [101]. Blood for BG measurement was also typically taken directly from an arterial line, and measured using an Arkray Super Glucocard$^{TM}$ II glucometer (Arkray, Minnesota, USA). Both SPRINT and STAR rely on closely-related models of the glucose-insulin system [148]. SPRINT was a paper-based protocol developed using the model to optimize recommended insulin and nutrition delivery based on measured BG and previous interventions [101]. However, in use, SPRINT could not explicitly calculate $S_I$, or forward-predict the outcomes of interventions although

it implicitly uses a crude surrogate [265]. In contrast, STAR implements the glucose-insulin model on tablet computer and therefore identifies $S_I$, allowing forward prediction of interventions to optimize treatments, directly manage the risk of hypoglycaemia and personalize care [128].

For both protocols in the Christchurch Hospital ICU, patients received a similar nutrition type. SPRINT patients are typically fed enterally with either Glucerna$^{TM}$ 1 Cal. (34.3% Carbohydrate, 16.7% Protein, 14.4 g/L Fibre, Abbott Labs, Illinois, USA) or Diabetic Resource (36% Carbohydrate, 24% Protein, 12 g/L Fibre, Nestle Health Science, Epalinges, Switzerland). Similarly, STAR patients are typically fed Glucerna$^{TM}$ Select (31% Carbohydrate, 20% Protein,21.1 g/L Fibre, Abbott Labs, Illinois, USA). Note all carbohydrate concentrations exclude indigestible fibre. All the formulas used are within 2-8% of total carbohydrate and protein content and thus provide very similar nutrition content and composition for the patients over all of the years. For both protocols, parenteral nutrition is used occasionally to supplement enteral nutrition when necessary.

For both protocols, the same ACCP guidelines are used to determine the patients daily calorific goal intake of 25 kcal/kg/day [156] and enteral nutrition is advised between 30% and 100% of this calorific goal [101], [128], although fixed nutrition rates and rates up to 120% of calorific goal were included in this study. The main difference between the SPRINT and STAR feeding regime was SPRINT modulated feeding in steps up to +/- 10% and effectively targeted 60-70% of calorific goal [101], whereas STAR modulated feeding in steps up to +/- 30% and targeted 100% of calorific goal [128]. Note, In Christchurch ICU patients are not weighed so ACCP caloric goal feed is approximated by first assuming an 80 kg individual and then modifying this value based on frame size (subjective), age and sex, see Section 7.2.1.2 *Christchurch Clinical Implementation.*

#### *5.2.3.2 Gyula Hospital ICU, Hungary*

Kálmán Pándy County Hospital (Gyula, Hungary), which is also a mixed medical ICU, has been using STAR since December 2011. This ICU is markedly different from Christchurch in terms of clinical GC practices. IV insulin is delivered via continuous infusion, and local nutrition guidelines specify aggressive early parenteral nutrition to supplement enteral nutrition to a similar goal feed rate of 25 kcal/kg/day. Patients are transitioned from parenteral to enteral nutrition as their stay

progresses, and STAR modulates both rates to obtain total delivery values between 30% and 100% of the daily goal.

Starting criteria for STAR in Gyula is also two successive BG measurements over 8.0 mmol/L within a 4-hour period, but is subject to the clinician's choice, depending on expected length of stay and severity of illness of the patient. This difference in patient selection can be seen in Table 5.3, with the Gyula cohort having much higher Acute Physiology And Chronic Health Evaluation (APACHE) II scores and ICU length of stay. BG is measured using the E77 Elektronika Dcont Optimum or Dcont Personal Glucometers (E77, Budapest, Hungary) with blood taken directly from an arterial line. It should be noted that only one STAR tablet is available for use in the Kálmán Pándy County Hospital, thus limiting the patient numbers and increasing the severity of illness of selected patients as it was typically used for the most ill patients.

### 5.2.4 Analysis and statistics

Mortality on GC was calculated by working out the number of patients that died while on the GC protocol or within 5 hours of the GC protocol ending. This statistic is used to identify patients for whom GC might have impacted their ICU mortality.

BG performance statistics are presented as median and IQR of individual patient mean and standard deviation values of BG, as per Finfer et. al. 2013 [137]. All hypoglycaemia and other rare occurrences were manually verified. Due to irregular sampling intervals, patient episode BG data was also analysed after linear interpolation at 60 min intervals, see Chapter 2 *Interpretation of Retrospective BG Measurements*. Note, minutely sampling was not used as this analysis was done before the prior chapter's analysis had been performed. Therefore, the interpolated BG performance statistics are also presented in median and IQR of individual episode's mean and standard deviations of BG, as above.

Mean hourly nutrition rates of glucose are reported, but exclude hours in which patients were not fed, as occasionally patients could not be fed due to clinical reasons irrespective of the GC protocol. The standardized mortality ratio (SMR) calculated in Table 5.2 was calculated using the APACHE

II Risk of Death prediction and the recorded hospital mortality. As the number of patients in the Gyula cohort (N=47) is significantly less than the Christchurch cohort (N=267) a p-test power calculation is performed to assess the comparison of raw ICU mortality.

Non-parametric statistics are used exclusively for all the comparative tests due to the typically skewed distributions of BG, insulin dose and other data. P-values were computed using the Mann -Whitney rank-sum test for all continuous data and the chi-squared test for categorical data. P-values $<0.025$ are considered statistically significant after Bonferroni correction [224] for multiple comparisons.

## 5.3 Results

### 5.3.1 STAR vs SPRINT Christchurch

The cohort demographics in Table 5.2 show the SPRINT and STAR Christchurch cohorts have no significant difference in gender, age, operative status, or ICU length of stay. However, the STAR cohort had higher APACHE II scores and ICU mortality rates than the SPRINT cohort.

Table 5.4 presents the cohort results of GC safety and performance for STAR and SPRINT in Christchurch. In targeting the 4.4-8.0 mmol/L range using model-predictive methods to personalize treatment, STAR reduced clinical workload in the same ICU (13.6 measurements per day per patient compared to 15.8, $P < 0.001$, Table 5.4) and increased nutrition delivery per-episode compared to SPRINT (Achieving 86% of ACCP calorific goal feed compared to 73%, $P < 0.001$, Table 5.5), when allowed to feed. It did so while maintaining consistent GC for a more critically ill cohort.

Table 5.5 presents the per-patient and per-episode GC safety and performance of STAR and SPRINT in Christchurch. These results show both STAR and SPRINT protocols resulted in over 86% time in the BG band of 4.4-8.0 mmol/L per-episode (86.6% and 93.0% respectively), while maintaining safe control of severe hypoglycaemia (BG $<$ 2.2 mmol/L, 1.5% vs. 0.3% of patients respectively). SPRINT's lower and tighter BG target range (4.4-6.1 mmol/L), resulted in an increased incidence of moderate hypoglycaemia (BG $<$ 4.0 mmol/L, 62.0% vs 26.3% of patients for SPRINT and STAR, respectively) compared to STAR.

### 5.3.2 STAR Christchurch vs STAR Gyula

The cohort demographics in Table 5.3 show the STAR Christchurch and Gyula cohorts have no significant difference in gender or age. However, STAR Gyula had much higher APACHE II scores (32 vs 21, $P < 0.001$), ICU length of stay (14 days vs 5.7 days, $P < 0.001$), and ICU mortality (38.3% vs 24.3, $P = 0.05$) than the STAR Christchurch cohort. All of these results are consistent with each other.

Despite a significant increase in the severity of illness, STAR demonstrated consistent effective GC performance over the Gyula cohort. Table 5.5 shows both Christchurch and Gyula STAR cohorts achieved over 86% of time in its target range (4.4–8.0 mmol/l) per-episode (86.6% and 87.1% respectively, P = 0.81), while maintaining very safe control of hypoglycaemia per-episode, BG < 4.4 mmol/L (0.0% and 0.9% of time respectively, P = 0.003).

Fig. 5.1 shows the STAR BG CDF in these two ICUs are almost identical, although P < 0.001 due to very large number of measurements. The per-patient BG mean and standard deviation was also very similar for both of the cohorts (7.0 vs. 6.9 and 1.5 vs. 1.6, respectively). Thus, this evidence suggests that STAR is able to deliver consistent GC to different cohorts with significantly different clinical practices and illness severity. The ability for the STAR controller stochastic model to capture both the variability seen in the Gyula and Christchurch cohort Chapter 3 *Evaluation and simplification of STAR's stochastic model* may largely account for why such similar GC performance and safety could be achieved in these two cohorts.

Table 5.4 presents the cohort GC safety and performance results of STAR in Christchurch and Gyula. Compared to Christchurch, the Gyula clinical staff chose to use longer intervention intervals (11.7 vs. 13.6 measurements per day, P < 0.001) and fed a significantly higher amount of glucose per-episode (5.1 vs 7.4 g/hr, P < 0.001, Table 5.5), largely due to their higher carbohydrate parenteral and enteral feed regime and/or composition. Thus, they required higher insulin dosing per-episode (2.7 vs 3.2 U/hr, P = 0.01, Table 5.5), amplifying the effects of $S_I$ variations [123]. This difference ultimately resulted in the Gyula cohort having a higher occurrence of moderate hypoglycaemia (26.3% vs 53.2% of patients BG < 4.0 mmol/L, P < 0.001).

Table 5.4: Cohort Glycemic Control (GC) results for the STAR and SPRINT cohorts in Christchurch and Gyula Hospital Intensive Care Unit (ICU).

| | SPRINT Chch | STAR Chch | STAR Gyula | P-value SPRINT Chch, STAR Chch | P-value STAR Gyula, STAR Chch |
|---|---|---|---|---|---|
| Number Patients | 292 | 267 | 47 | - | - |
| Number Episodes | 355 | 336 | 47 | - | - |
| Total Hours | 40931 | 22948 | 6244 | - | - |
| Number of BG Measurements | 26530 | 12363 | 3050 | - | - |
| Median [IQR] Days on protocol | 3.0 [1.3 : 6.3] | 1.9 [0.9 : 3.5] | 3.9 [1.9 : 6.9] | <0.001 | <0.001 |
| Median [IQR] Measures/day per-patient | 15.8 [14.1 : 18.0] | 13.6 [11.5 : 16.2] | 11.7 [10.9- 13.3] | <0.001 | <0.001 |
| Glycaemic Performance – Cohort Raw Data | | | | | |
| BG Mean | 5.8 | 7 | 6.8 | - | - |
| BG SD | 1.3 | 1.3 | 1.3 | - | - |
| BG Median [IQR] | 5.7 [5.0 - 6.6] | 6.8 [6.0 - 7.9] | 6.7 [5.8 – 7.8] | <0.001 | <0.001 |
| Glycaemic Performance -Cohort Hourly Interpolated | | | | | |
| BG Mean | 5.7 | 6.7 | 6.6 | - | - |
| BG SD | 1.2 | 1.2 | 1.2 | - | - |
| BG Median [IQR] | 5.6 [5.0 - 6.4] | 6.6 [6.0 - 7.4] | 6.5 [5.9 - 7.2] | <0.001 | <0.001 |
| % time >10.0 mmol/l | 1.5 | 4.4 | 3 | - | - |
| % time 4-6.1 mmol/l (SPRINT Target) | 71.4 | 43.9 | 46.5 | - | - |
| % time 4.4-8.0 mmol/l (STAR Target) | 87.2 | 82.6 | 85.7 | - | - |
| % time <4.4 mmol/l | 7.4 | 1.4 | 1.9 | - | - |
| % time <4.0 mmol/l | 2.5 | 0.6 | 0.9 | - | - |
| % time <2.22 mmol/l | 0.002 | 0.004 | 0 | - | - |

*blood glucose (BG), standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

Table 5.5: Per-patient and Per-episode Glycemic Control (GC) results for the STAR and SPRINT cohorts in Christchurch and Gyula Hospital Intensive Care Unit (ICU).

| | SPRINT Chch | STAR Chch | STAR Gyula | P-value SPRINT Chch, STAR Chch | P-value STAR Gyula, STAR Chch |
|---|---|---|---|---|---|
| Number Patients | 292 | 267 | 47 | - | - |
| Number Episodes | 355 | 336 | 47 | - | - |
| Glycaemic Performance - Per-Patient Raw Data | | | | | |
| Median [IQR] BG mean | 5.9 [5.5 - 6.3] | 7.0 [6.6 - 7.6] | 6.9 [6.6 - 7.4] | <0.001 | 0.60 |
| Median [IQR] BG SD | 1.2 [1.0 - 1.6] | 1.5 [1.2 - 2.1] | 1.6 [1.3 - 1.9] | <0.001 | 0.50 |
| Median [IQR] BG median | 5.7 [5.3 - 6.1] | 6.7 [6.3 - 7.3] | 6.6 [6.3 - 7.1] | <0.001 | 0.28 |
| # (%) Patients <4.0 mmol/l | 181 (62.0%) | 70 (26.3%) | 25 (53.2%) | <0.001 | <0.001 |
| # (%) Patients <2.22 mmol/l | 1 (0.3%) | 4 (1.5%) | 2 (4.3%) | 0.20 | 0.22 |
| Glycaemic Performance – Per-Episode Hourly Interpolated | | | | | |
| Median [IQR] BG mean | 5.8 [5.4 - 6.2] | 6.7 [6.4 - 7.3] | 6.7 [6.5 - 7.1] | <0.001 | 0.60 |
| Median [IQR] BG SD | 1.1 [0.8 - 1.5] | 1.2 [0.9 - 1.7] | 1.3 [1.04 - 1.5] | 0.002 | 0.23 |
| Median [IQR] BG median | 5.6 [5.2 - 6.0] | 6.5 [6.2 - 7.0] | 6.5 [6.3 - 6.7] | <0.001 | 0.61 |
| % time >10.0 mmol/l | 0.0 [0.0 - 1.6] | 1.6 [0.0 - 6.5] | 2.4 [0.7 - 5.4] | <0.001 | 0.16 |
| % time 4-6.1 mmol/l (SPRINT Target) | 65.6 [52.4 - 77.9] | 29.8 [12.4 – 45.9] | 33.3 [21.5 - 40.9] | <0.001 | 0.49 |
| % time 4.4-8.0 mmol/l (STAR Target) | 93.0 [85.0 - 97.5] | 86.6 [75.0 - 94.1] | 87.1 [79.3 - 91.1] | <0.001 | 0.81 |
| % time <4.4 mmol/l | 7.3 [2.1 - 16.1] | 0.0 [0.0 - 1.8] | 0.9 [0.0 - 2.8] | <0.001 | 0.003 |
| % time <4.0 mmol/l | 1.4 [0.0 - 5.71] | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 1.8] | <0.001 | <0.001 |
| % time <2.22 mmol/l | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] | 0.97 | 0.71 |
| Intervention Performance – Per-Episode (Excluding not fed) | | | | | |
| Median [IQR] Mean Insulin (U/hr) | 2.2 [0.0 - 2.8] | 2.7 [1.9 - 3.5] | 3.2 [2.4 - 4.6] | <0.001 | 0.01 |
| Total Hours not fed (%) | 16430 (40.1%) | 2305 (10.0%) | 0 (0.0 %) | - | - |
| Median [IQR] Mean Goal Feed (%) | 73 [52 - 86] | 86 [64 - 97] | 80 [74 - 88] | <0.001 | 0.28 |
| Median[IQR] Mean Total Glucose (g/hr) | 4.2 [3.1 - 5.4] | 5.1 [4.0 - 6.2] | 7.4 [6.2 - 8.9] | <0.001 | <0.001 |
| Median [IQR] Mean Enteral Glucose (g/hr) | 4.1 [3.0 - 5.3] | 4.5 [2.6 - 5.6] | 3.04 [1.48 - 5.40] | 0.74 | 0.09 |
| Median [IQR] Mean Parenteral Glucose (g/hr) | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 1.1] | 4.05 [2.84 - 5.69] | <0.001 | <0.001 |

*blood glucose (BG), standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

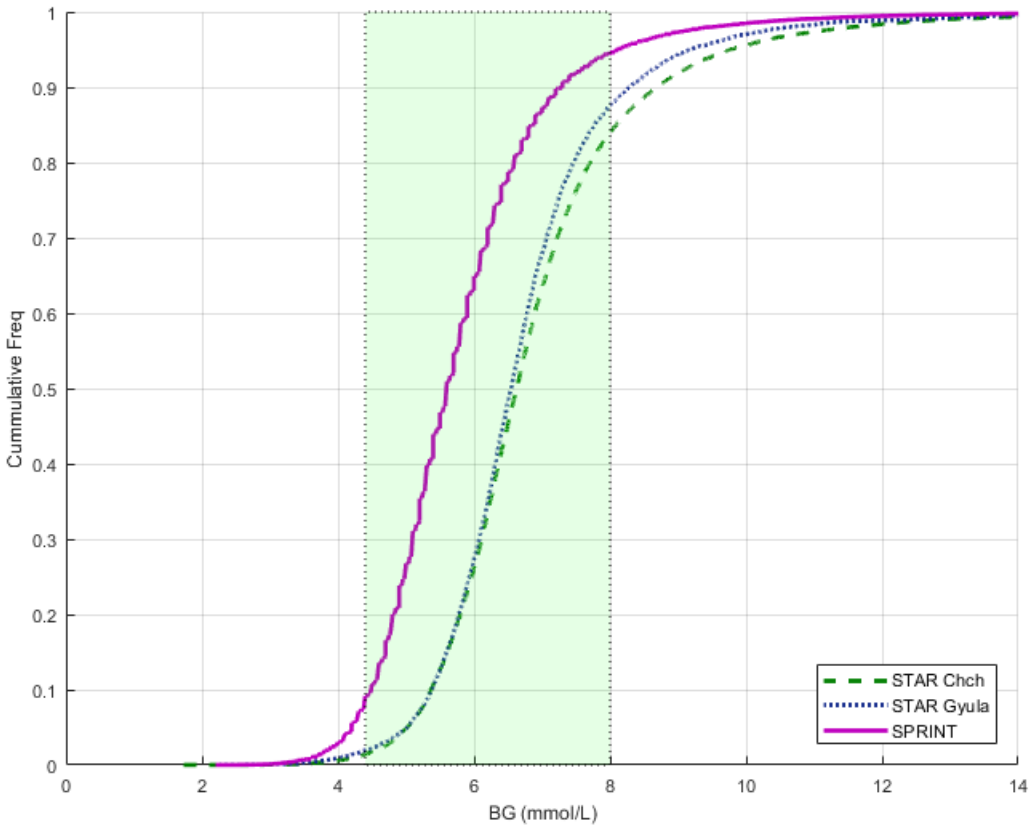



Figure 5.1: CDF plots comparing the STAR Christchurch, STAR Gyula, SPRINT Christchurch cohorts hourly resampled blood glucose (BG). The target BG band 4.4–8.0 mmol/L is shown in the green shaded region.

## 5.4 Discussion

### 5.4.1 Cohort Demographics

Table 5.2 suggests a shift in severity of illness in the Christchurch ICU over the past 7 years, with the patients on STAR being more critically ill on average than those on SPRINT and a lower surgical rate indicating more acute cases. This phenomenon is not wholly unexpected. Increasing economic and demographic stress worldwide has placed greater demand on limited bed spaces. In highly occupied units like Christchurch (2.2 beds/1000 people) admission may be limited to the more critically ill [266].

The increase in ICU mortality in patients on STAR compared to SPRINT is likely a result of the increase in severity of illness in the STAR cohort. The hospital SMR reported in Table 5.2, shows an increase between the SPRINT and STAR Christchurch cohorts (0.76 vs 0.86, respectively). This result suggests the APACHE II risk of death scores are slightly more representative of the cohort's illness in the STAR cohort compared to the SPRINT cohort. The significant difference in the severity of illness between the STAR Gyula and Christchurch cohorts is largely due to the different entrance criteria, as only one STAR tablet computer is available and STAR is thus reserved for the more critically ill patients, as clinically selected.

### 5.4.2 STAR versus SPRINT

Compared to SPRINT, both STAR cohorts had slightly lower time in the 4.4-8.0 mmol/L band per-episode (86.6% and 87.1% vs. 93.0%). SPRINT targeted a lower and tighter range (4.4-6.1 mmol/L), resulting in an increased incidence of moderate hypoglycaemia (BG $<$ 4.0 mmol/L, 62.0% vs 26.3% and 53.2% of patients having at least one occurrence) compared to STAR. In addition, SPRINT measured more frequently However, recent studies have shown that time in the essentially same band, 3.9-7.8 mmol/L, is associated with improved outcomes [61], [142], [261], supporting this slightly higher upper target limit of 8.0 mmol/L.

Flexibility to patient specific requirements is a critical aspect of the STAR model-based protocol, as the tablet application allows nursing staff to enter any information that may change the patient's

insulin or nutrition requirements. This approach allows STAR to adapt to patient-specific needs and provide appropriate recommendations that take into account all necessary considerations. However, the effect this has had on protocol compliance has not yet been investigated.

SPRINT was deliberately designed to target nutrition to 60-70% or lower for control, which reduced insulin requirements and thus risk of hypoglycaemia [31], [265]. SPRINT had a maximum 2-hourly measurement rate for the same reasons of risk mitigation which increased workload relative to STAR's 3-hourly maximum. In addition, the tighter SPRINT target (4.4-6.1 mmol/L) is also part of the reason for this increased nurse workload and lower feeding on SPRINT. For STAR, the use of stochastic risk models [145], [149] and virtual patient design in-silico [154], [230] enabled the lower workload, and also play a role in making possible the higher nutrition delivery, although a wider overlapping target band also enables some of this increased nutrition

Both STAR and SPRINT Christchurch have the same starting and stopping criteria. However, patients on STAR Christchurch required insulin therapy for 36.7% fewer days than SPRINT ($P < 0.001$, Table 5.4). Differences that could account for this significant reduction in length of treatment for a more critically ill cohort include:

- Significantly reduced incidence of moderate hypoglycaemia (BG $<$ 4.0 mmol/L) with STAR.
- Slightly higher median BG with STAR, with similar BG in the 4.4-8.0 mmol/L range.
- Increased mortality on the STAR protocol.
- Increased amount of carbohydrate, protein, fibre and nutrition content delivered by STAR.

The number of patients experiencing moderate hypoglycaemia are not enough to account for the size of this change. Prior analyses have suggested that a high percentage of time, per-patient, in target bands very similar to STAR is beneficial [61], [142], [261]. Despite the lower median BG for SPRINT, the time in the 4.4-8.0 mmol/L band is very similar for both protocols. ICU and hospital mortality were higher for STAR due to changes in the illness severity and demographic factors, as seen in Table 5.2. However, the percentage mortality while on the respective GC protocol is very similar (5.5% vs 6.4%, $P = 0.72$, Table 5.2), suggesting that the reduction in period of GC is less likely to be attributed to the cohorts respective mortality. This outcome leaves the increased

carbohydrate, protein, fibre and overall nutrition intake as a potential reason for the reduced length of GC. However, there is significant debate about the role of energy and protein delivery in critical illness [136], with some literature showing increased calorific intake levels that are still below the 100% calorific goal have beneficial effects [267] and others showing no effect [134]. In this study, the median per-episode feed for the STAR Christchurch cohort was 86% of calorific goal feed, shown by Heyland et al. [135] to be a region of reduced risk of death.

### 5.4.3 STAR Christchurch versus STAR Gyula

STAR entry criteria were the same in both units based on hyperglycaemia (BG $>$ 8.0 mmol/L) or clinician choice. STAR was used for a patient through their entire stay or multiple episodes of stay in Gyula, and is the standard of care for the Christchurch ICU for all GC. Hence, the study, while a retrospective analysis, is run essentially prospectively in that all patients who had STAR with the same target band were included from each unit.

One difference between Gyula and Christchurch cohorts is that with a single tablet to run STAR in Gyula, clinician's chose the more ill patients they thought would benefit. This choice could likely have biased the severity of illness upwards, as well as the length of stay (Table 5.3). It may have similarly affected the difference in ICU mortality in Table 5.3, although this comparison is significantly underpowered given the low patient numbers in Gyula and could thus also be due to statistical variation. Hence, variation in these cohorts is biased by this choice and the results in Table 5.3 could be due to one or a combination of these factors. However, a recent study by Uyttendale et. al [255] has shown that mortality is independent of patient variability, thus does not effect a protocol's ability to provide GC. Therefore, this difference is not as relevant to showing that STAR can provide safe, effective GC results across very different patients and clinical practices.

In the STAR Christchurch cohort, 4 patients experienced severe hypoglycaemia and in the Gyula cohort 2 patients experienced severe hypoglycaemia. STAR's model-based predictive GC forward predicts potential patient-specific behaviour using the 5th and 95th percentile, choosing an intervention to optimize the placement of these stochastic bounds [128], [145]. Therefore, all of the hypoglycaemic cases occurred outside of STAR's cohort based model-predictive bounds. Each of these patients had

a 99th percentile (outlier) patient-specific model-based insulin sensitivity during their hypoglycaemic episode and the number of events suggest this is a 1 in 100 event, which broadly matches the cohort results observed in Table 5.5.

It is worth noting that all of the severe hypoglycaemic events on STAR, in Christchurch, occurred at high fixed nutrition rates over 100% of ACCP goal feed, but $< 120\%$. High fixed nutrition rates raise BG all else equal, resulting in the need for higher or maximum insulin rates to control hyperglycaemia. The large amount of insulin in the patient then amplifies any small changes in the patient's $S_I$ due to changes in condition, significantly reducing the ability to control BG safely and effectively [123]. Despite high fixed nutrition inputs, up to 120% goal feed in some cases, making GC more difficult, it also is an important feature of the STAR application allowing it to be more flexible to specific clinical needs. However, in these specific cases lower (100% or less) and/or variable nutrition would have allowed greater safety [128].

### 5.4.4 Limitations

A total of 19 patients were excluded from the STAR Christchurch (15) and Gyula (4) analysis as they received more than 120% of ACCP recommended caloric target on average. In some instances the high level of nutrition may be clinically specified. However, in most cases the high level of nutrition is due to nursing staff choosing to fix enteral and/or parenteral feed on STAR.

The discrepancy in patient numbers between the two STAR cohorts, over approximately the same time period, is due to only one of STAR tablet being available in Gyula, compared to 10 in Christchurch. The number of patients in the Gyula cohort is low. Therefore, there is not yet have enough power (52%, p-test) for comparison to the Christchurch cohort in relation to raw mortality on the STAR GC protocol in Gyula, or morbidity and per-patient BG statistics (e.g. per-patient TIB, mean/median BG). Sufficiently more patients would be required for a well powered outcome study on mortality or morbidity.

It should be noted that there was also patient selection bias for STAR Gyula, creating significantly different cohorts in terms of ICU length of stay and severity of illness ($P < 0.001$, Table 5.3). The

difference in the cohorts could result in GC being more complex or simpler in the Gyula cohort relative to the Christchurch cohort due to more severely ill patients having more complications or possibly longer length of stay patients being more stable. However, it also enables generalisability and repeatability of STAR to be shown over very different cohorts.

As mentioned previously, STAR and SPRINT target different BG bands (4.4-8.0 mmol/L and 4.4-6.1 mmol/L, respectively). These BG targets overlap, but vary in width and level of BG. Therefore, the comparison of these two protocols in terms of percentage of time in 4.4-8.0 mmol/L BG band may be an unfair statistic considering that only one the protocols actually targeted this band. The only way to fully and fairly compare the two protocols performance would be if they both targeted the same BG target.

To compare the STAR GC protocol to other ICU GC protocols is difficult as the cohorts need to be similar and the same statistics need to be reported, as seen in Section 1.2.3 *Glycaemic Control Protocols*. Considering performance, safety and workload to achieve them, that other studies have shown similar performance based on time in band [129], [138], [214], [268]. STAR achieved these performance and safety results with a lower relative clinical workload over a much larger, more diverse and relatively very ill cohort. With the data available, it appears STAR performs very well in comparison to other current ICU GC protocols with better safety and lower workload. However, a best protocol cannot be determined without the same statistics being reported and the cohorts being much more similar.

Sensor error can affect the quality of control [269], particularly in target to value protocols [270]. SPRINT was designed in silico to be robust to these errors for the Arkray Super Glucocard$^{TM}$ II glucometers used (CV approximately 9.35 % [256], [257]). STAR is more robust to this error due to its target to range approach, using the $5^{th}$ and $95^{th}$ percentile of the $S_I$ stochastic model, to guide robust control. In addition, Christchurch Hospital ICU changed to the more reliable Accu-Chek Infor II glucometer in 2012 (CV approximately 6.0% [258], [259]). The Gyula unit used a E77 Elektronika Dcont Optimum or Dcont Personal Glucometers (CV $< 4.6\%$).

As seen previously in Chapter 2 *Interpretation of Retrospective BG Measurements*, minutely interpolation resulted in the best representation of a GC protocols BG performance statistics. However, minutely interpolation was not used in this analysis as the research into interpolation occurred after this research had been completed. As a consequence the BG percentage of time out of the targeted band statistics may be slightly conservative, although very unlikely to be significant, see Chapter 2.

By using model-based predictive GC tailored to patient-specific metabolic response, through identifying their respective time variant $S_I$, safe and effective GC can be offered. With the stochastic models of $S_I$ variability used, Chapter 3 *Evaluation and simplification of STAR's stochastic model*, STAR thus directly manages inter- and intra- patient variability to improve safety. Other protocols could have failed in the past due to their inability to adjust for this inter- and intra- patient variability via model-based GC on a computer. Considering this study is a retrospective analysis, as opposed to a randomized control trial, we cannot explicitly link the outcomes to GC. Hence, the main focus of this study is to demonstrate that safe, effective and generalizable GC is possible. To this end, STAR is also currently undergoing a clinical trial at the International Medical University Medical Centre, Kuala Lumpur, Malaysia, furthering investigating it's generalisability across ICUs.

## 5.5 Summary

This retrospective, observational study analysed the GC safety, performance and generalizability of the STAR protocol in Christchurch, NZ and Gyula, Hungary. Results of STAR's predecessor, SPRINT, were presented for comparison. Patients on the STAR protocol spend over 86% of all time on protocol within the goal 4.4-8.0 mmol/L BG band, with very few occurrences of severe or moderate hypoglycaemia. STAR outperformed SPRINT by providing higher nutrition and safe, effective control for all days of stay, as well as reducing time on protocol and workload.

Overall, in Christchurch, the STAR framework has shown an ability to adapt well to a wide range of situations, and provide safe and effective treatment at all times. It has also reduced clinical burden in the ICU, by lowering the number of measurements and interventions needed to achieve equivalent control to SPRINT, while improving safety.

A key criteria for success in any protocol is the ability to demonstrate high performance and high safety across patient types, time, clinical practice culture, and clinical resources. The results of the STAR protocol in Gyula, Hungary are used to analyse this criteria. The results show STAR comprehensively meets these criteria, with the BG distributions of the two cohorts being almost identical even though the clinical practices are significantly different. Thus, this research shows how a model-based and personalized approach to GC can safely improve care and reduce workload across differing clinical practices.

The retrospective results prove STAR is a promising GC protocol clinically, with greater generalisability than other published protocols. However, further investigation into protocol compliance is required to ensure this outcome is a result of the protocol and not clinical staff involved. In addition, further investigation into nutrition feeding protocols is required, as fixed feeding was consistently present when hypoglycaemia occurred, counter to STAR's normal use, and is an area of concern for clinicians.

# Chapter 6

# Compliance of the STAR Glycaemic Control Protocol

## 6.1 Background

As discussed previously in Section 1.2 *Glycaemic Control in the Intensive Care Unit*, the benefit of GC is still heavily debated, with mixed evidence shown for both cases [264]. Before the physiological benefits and/or consequences of GC can be assessed, effective GC needs to be achieved clinically, reducing both hyper- and hypo- glycaemia [260] . Some previous attempts of GC have failed due to increased occurrence of hypoglycaemia and/or not effectively reducing the prevalence of hyperglycaemia [103], [105], [107], [108], [110], [111], [213]. These issues hinder the ability to see the potential physiological benefit of GC. The poor performance of these previous attempts at GC may not necessarily be due to the theoretical implementation of the GC protocol, but the clinical impracticality of the GC protocol and resulting poor clinical staff compliance to the protocol [151], [271], [272].

GC protocol adherence can be very protocol specific, depending on the clinical demands and flexibility of the protocol, and has been shown to be directly related to the resulting GC performance

[1] **K. W. Stewart**, J. Dickson, C. Pretty, F. Thomas, G. Shaw, and J. G. Chase, "High Compliance = Good Control? Compliance of the Stochastic TARgeted (STAR) Glycemic Control Protocol," in 15th Annual Diabetes Technology Meeting, 2015.

[138], [273]. Therefore, for a GC protocol to be clinically effective it must both be practically implementable, in terms of workload and clinical flexibility, while still being able to provide safe and effective GC. Only once this outcome is achieved can the potential physiological benefits of GC be investigated.

The tablet-based STAR GC protocol has been designed to be clinically flexible and still provide patient-specific GC [128], [147]. STAR uses a clinically evaluated pharmaco- kinetic and dynamic model of the insulin-glucose system [31], [148] and a cohort based model of $S_I$ variability [145], [149] to compute the optimal patient-specific insulin and nutrition interventions which maximize time in targeted band, and nutrition, while maintaining a maximum 5% risk of BG $< 4.4$ mmol/L [128], [147]. STAR adapts to nurse workload by allowing variable 1-3 hourly BG measurement frequencies, selected (largely) by nurses. In addition, if clinical circumstances arise, resulting in STAR's GC intervention not being able to be followed, STAR is able to adapt future treatments to this limitation, furthering its clinical flexibility. As seen in Chapter 5 *Clinical performance review of the STAR Glycaemic Control protocol*, STAR is able to provide patient-specific, safe and effective GC. However, an investigation into protocol compliance is required to ensure this outcome is a result of the protocol and not clinical staff involved.

The aim of this retrospective analysis is to review the compliance of STAR data input, and recommendations. Clinical bedside sheets are reviewed for data input reference and the recommendations recorded by STAR are used to assess recommendation compliance. The results of this analysis will assess the clinical practicability of the STAR protocol and allow clinically impractical areas to be addressed.

## 6.2 Methods

### 6.2.1 STAR Tablet Protocol

Starting criteria for STAR in the Christchurch Hospital ICU, NZ is two successive BG measurements over 8.0 mmol/L within a 4 hour period. IV insulin is delivered in hourly bolus form, with added background infusions of up to 3.0 U/h when insulin requirements are high and sustained [128], [147]. EN interventions are changed by STAR, in maximum steps of ±30% of the patients daily caloric goal [128]. ACCP guidelines are used to determine the patients daily caloric goal intake of 25 kcal/kg/day [156] and EN is advised between 30% and 100% of this caloric goal [128]. PN interventions are not changed by STAR, and are only changed at the clinical staff's discretion. However, PN interventions are still required to be recorded by STAR. Blood for BG measurement is typically taken directly from an arterial line and measured using a PoC BG meter.

STAR makes recommendations to clinical staff based on a patient's, model identified, current and predicted future metabolic state captured by $S_I$. If a patient's BG is currently within the targeted BG band (typically 4.4-8.0 mmol/L), clinical staff have the flexibility to choose between 1-3 hour measurement intervals. However, if a patient's BG is outside the targeted BG band, clinical staff are limited to hourly measurements. After every BG measurement, clinical staff are required to enter BG information, and enter/confirm insulin and nutrition information. The STAR software framework is designed to be very flexible allowing clinical staff to modify and/or add historical information, and also change the intervention given from what STAR recommended due to interfering clinical circumstances [274], [275].

### 6.2.2 Patient Data

Clinical data for compliance analysis was obtained from 221 patients treated with the STAR GC protocol in Christchurch Hospital ICU, NZ [215]. A randomly chosen subset of 20 patients was chosen from this cohort for data entry compliance assessment. A smaller cohort was chosen due to the labour involved with manually checking paper-based records. The entire cohort was used for assessment of recommendation compliance. The Patient demographics for both cohorts can be

seen in Table 6.1. The Upper South Regional Ethics Committee, New Zealand granted approval for the retrospective audit, analysis and publication of the Christchurch patient data. Note, a single patient may be treated by the protocol on several distinct occasions separated by significant breaks. Therefore, a distinction is made between a patient and an episode of GC, see Section 5.2.2.3 *Episodes of GC*.

Table 6.1: Demographic data of the cohorts used for STAR protocol compliance assessment.

| | STAR Chch Cohort | STAR Sub-cohort | P-Value |
|---|---|---|---|
| *Patient Demographics* | | | |
| Num Episodes: | 286 | 33 | - |
| Num Patients: | 221 | 20 | - |
| Age [IQR]: | 64.00 [54.00 - 72.00] | 67.50 [53.50 - 76.00] | 0.54 |
| Gender (% Male): | 66.1 | 60.0 | 0.63 |
| ICU Length of Stay (Days) [IQR]: | 8.43 [3.14 - 15.33] | 9.49 [3.04 - 12.22] | 0.89 |
| Days on Protocol [IQR]: | 2.67 [1.50 - 5.67] | 6.67 [1.77 - 9.67] | - |
| Percent Operative: | 29.0 | 35.0 | 0.61 |
| APACHE II Score [IQR]: | 21.00 [16.00 - 27.00] | 20.00 [14.00 - 22.00] | 0.25 |
| Overall ICU Mortality (%): | 28.1 | 5.0 | 0.03 |
| Overall Hospital Mortality (%): | 33.0 | 10.0 | 0.04 |
| Mortality on GC (%): | 7.7 | 0 | 0.37 |
| *GC Performance Statistics per patient* | | | |
| BG mean (mmol/L): | 6.66 [6.36 - 7.21] | 6.86 [6.57 - 7.49] | 0.04 |
| BG SD (mmol/L): | 1.17 [0.85 - 1.65] | 0.96 [0.74 - 1.44] | 0.07 |
| % time BG >10.0 mmol/L | 1.22 [0.00 - 5.56] | 0.00 [0.00 - 6.25] | 0.85 |
| % time BG within 4.0-8.0 mmol/L | 88.42 [77.42 - 94.44] | 89.86 [73.94 - 95.54] | 0.89 |
| % time BG <4.4 mmol/L | 0.00 [0.00 - 1.79] | 0.00 [0.00 - 0.00] | 0.02 |
| % time BG <2.22 mmol/L | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.74 |

*inter-quartile range (IQR), Acute Physiology And Chronic Health Evaluation (APACHE), Glycemic Control (GC), blood glucose (BG), standard deviation (SD). Data presented in Median [IQR] where appropriate.

### 6.2.3 Compliance Assessment

The manner in which data is recorded by the STAR tablet and the flexibility integrated into the STAR software creates two areas of compliance:

**Data entry compliance:** Tablet data entry matches what was recorded on the bedside sheet. Note, this is the 'official'/'legal' record for the ICU patient.

**Recommendation compliance:** STAR's recommendations matches what was recorded by STAR as having been given.

#### *6.2.3.1 Data entry compliance*

Bedside sheets were collected for 20 randomly chosen patients from Christchurch Hospital ICU, NZ. The data collected from the bedside sheets was then directly compared to the information collected from the STAR tablets (BG, insulin, and nutrition values). Cross referencing these two records can result in 3 different cases:

**Case 1:** Both records have a value present at a similar point in time:

$(t_{STAR} - 60) \leq t_{Bedside} \leq (t_{STAR} + 30)$

Therefore, the recorded values can be directly compared.

**Case 2:** STAR has a recorded data point, but no bedside sheet data exists around this point in time.

**Case 3:** The bedside sheet has a recorded data point, but no STAR data exists around this point in time.

Note, the STAR tablet records interventions to the nearest minute and you can typically expect around ±10-15 minutes delay between recording and the actual intervention [276]. In contrast, the bedside sheet only records interventions to the nearest hour. To account for this difference, a timing tolerance was added when matching up interventions. A STAR tablet data point was considered to match a bedside sheet data slot if it occurred up to an hour after the bedside data slot to account for truncation of time, where for example the STAR recorded time of 13:42 → bedside sheet slot of 13:00. Equally, a STAR tablet data point was considered to match a bedside sheet data slot if it

occurred up to half an hour before the bedside data slot to account for rounding up of time, where for example the STAR recorded time of 13:42 → bedside sheet slot of 14:00.

All of the cases mentioned above can occur in BG measurements and interventions given (Insulin, EN, and PN). As it is difficult to state whether absence or presence of data is non-compliant (Case 2 and 3), the main focus of this analysis will be on matched measurements (Case 1). However, the absence and presence of data will still also be reported. When comparing nutrition interventions a tolerance of ±0.05 mmol/min was used to allow for small discrepancies in the nutrition content given. No tolerance was given for the BG measurements and insulin interventions.

This analysis assumes all the data recorded on the bedside sheets is correct. Any absence of data on the bedside sheet was assumed to be zero for lack of better knowledge. Note, this may limit the validity of some of the intervention compliance results, such as in interventions that are held constant i.e. insulin infusions and/or nutrition interventions.

#### *6.2.3.2 Recommendation compliance*

STAR tablet data was recorded for 221 patients in Christchurch Hospital ICU. The recommendations provided by STAR at each intervention is recorded by the tablet. These recommendations can then be directly compared to the data input into the STAR tablets (BG, insulin and nutrition values). Using this information a compliance to the STAR GC protocol recommendations can be determined. It should be noted that a deviation from STAR's recommendation may not represent non-compliance, but could be a result of clinical circumstances resulting in the intervention unable to be undertaken.

## 6.3 Results

### 6.3.1 Data entry compliance

The 20 bedside sheet review showed high compliance in all interventions, with both BG and insulin interventions approximately 94% compliant. Both nutrition interventions had slightly lower compliance of approximately 87%, and a large spread per-patient with an IQR of 20.6% and 47.2%, for EN and PN respectively. In addition, when non-compliance did occur in any intervention, particularly BG measures and EN interventions (+0.2 mmol/L and +0.05 mmol/L), it was only a small difference. Percentages of missing data in STAR or on the bedside was approximately none, median differences for all cases being 0.0%, with the largest discrepancy being in the EN intervention information (0.5%).

Table 6.2: STAR protocol data entry compliance results of the 20 patient STAR sub-cohort.

| | |
|---|---|
| *Matched Data Compliance* | |
| Number Bedside Sheets | 20 |
| Number Hours | 3634 |
| Number Measurements | 1557 |
| *Percentage input compliance per-patient* | |
| BG Measures (%) | 94.7 [93.3 : 96.2] |
| Insulin Doses (%) | 94.8 [93.8 : 98.2] |
| EN Interventions (%) | 86.5 [76.8 : 97.4] |
| PN Interventions (%) | 88.2 [52.6 : 99.8] |
| *Total number of non-compliant interventions* | |
| BG Measures | 67 |
| Insulin Doses | 306 |
| EN Interventions | 298 |
| PN Interventions | 231 |
| *Non-compliant intervention differences (= STAR Data − Bedside Data)*** | |
| BG Measurement (mmol/L) | 0.2 [-0.1 : 0.7] |
| Insulin Dose (mU/min) | 500.0 [-16.7 : 3016.7] (18.5 [-0.6 : 111.8] %) |
| EN Intervention (mmol/min) | 0.05 [-0.14 : 0.13] (13.2 [-36.8 : 34.2] %) |
| PN Intervention (mmol/min) | -0.20 [-0.26 : -0.15] (-50.0 [-65.0 : -37.5] %) |
| *Percentage on Bedside and NOT on STAR* | |
| BG Measures (%) | 0.0 [0.0 : 1.8] |
| Insulin Doses (%) | 0.0 [0.0 : 0.6] |
| EN Interventions (%) | 0.5 [0.0 : 1.5] |
| PN Interventions (%) | 0.0 [0.0 : 2.9] |
| *Percentage on STAR and NOT on Bedside* | |
| BG Measures (%) | 0.0 [0.0 : 1.8] |
| Insulin Doses (%) | 0.0 [0.0 : 0.3] |
| EN Interventions (%) | 0.0 [0.0 : 0.8] |
| PN Interventions (%) | 0.0 [0.0 : 0.0] |

*blood glucose (BG), enteral nutrition (EN), parenteral nutrition (PN). Data presented in Median [inter-quartile range (IQR)] where appropriate. **Relative differences based on median values in Chapter 5 *Clinical performance review of the STAR Glycaemic Control protocol.*

### 6.3.2 Recommendation compliance

Both cohorts had extremely good recommendation compliance, with all of STAR's recommendations being changed very infrequently, as shown in Table 6.3. In addition, when interventions were changed it was either to decrease the insulin bolus given by 1.0 U, increase the insulin infusion by 1.0 U or increase the EN and PN feed rate by approximately (20 mL/hr). Similar to the data entry compliance, both nutrition recommendations had a lower, lower quartile compliance. The median and IQR for all interventions of both cohorts is similar, suggesting the STAR sub-cohort represents the compliance of the entire STAR cohort relatively well.

Table 6.3: STAR protocol recommendation compliance results for the entire STAR cohort and sub-cohort.

| | STAR Chch cohort | STAR Sub-cohort |
|---|---|---|
| Number of Patients | 221 | 20 |
| Hours | 16,834 | 3,837 |
| Number Measurements | 8,833 | 1,836 |
| *Per-patient percentage recommendation compliance* | | |
| Insulin Bolus (%) | 100.0 [100.0 : 100.0] | 100.0 [100.0 : 100.0] |
| Insulin Infusion (%) | 100.0 [100.0 : 100.0] | 100.0 [100.0 : 100.0] |
| EN (%) | 100.0 [96.3 : 100.0] | 99.0 [97.1 : 100.0] |
| PN (%) | 100.0 [98.8 : 100.0] | 100.0 [99.0 : 100.0] |
| *Total number of recommendations changed* | | |
| Insulin Bolus | 22 | 3 |
| Insulin Infusion | 10 | 1 |
| EN | 120 | 37 |
| PN | 6 | 2 |
| *Changed interventions differences (= Recommended − Given)* | | |
| Insulin Bolus (U/hr) | 1.0 [-1.0 : 2.0] | 1.0 [-2.8 : 1.7] |
| Insulin Infusion (U/hr) | -1.0 [-2.0 : 1.0] | -1.0 [-1.0 : -1.0] |
| EN (ml/hr) | -20.0 [-24.0 : -7.7] | -16.0 [-20.0 : 1.8] |
| PN (ml/hr) | -15.0 [-80.0 : 20.0] | -20.0 [-20.0 : -20.0] |

*enteral nutrition (EN), parenteral nutrition (PN). Data presented in Median [inter-quartile range (IQR)] where appropriate.

## 6.4 Discussion

### 6.4.1 Data entry compliance

All matched interventions had a median patient compliance greater than 86% (Table 6.2), with both insulin and BG interventions being greater than 94.7%. In addition, when non-compliance did occur in any intervention, it was likely to be very small. Equally, there was approximately no bedside sheet information not entered into the STAR tablet, and vice-versa, with the median patient for all cases being approximately 0.0%. Therefore, the information entered into STAR by clinical staff was extremely good, and the large majority of recorded data can be considered true and accurate.

The lowest and largest range of data entry compliance was seen in both EN and PN interventions (Median patient 86.5% and 88.2%, Table 6.2). This suggests there may be issues around the recording of all nutritional interventions. However, as only EN interventions are changed by STAR, and PN interventions are up to the clinical staff's discretion, only poor EN compliance can be a result of GC protocol non-compliance. The lower compliance on the EN interventions could be due to:

1. Changing feed frequently is difficult and/or impractical to do in the clinical setting. Resulting in clinical staff finding it easier to leave the feed rate constant, while the STAR tablet believes it is changing, as evidenced by the variable EN intervention differences, Table 6.2. In addition, during the normal practice of ICU patient care, a patient's feed rate is usually kept constant, infrequently being stopped or reduced due to clinical circumstances or gastric tolerance. Thus, frequent changing of feed rate for GC is foreign practice.
2. There is a negative stigma around changing/lowering a patient's feed rate due to not receiving their prescribed ACCP caloric goal. Although, the lowering of feed rate by STAR is usually for a very short time period (Typically 3-5 hours), and the feed rates achieved overall are a median of 86%, per-patient [215]. However, if this were true the EN intervention differences would be consistently negative, Table 6.2, which they are not.

3. Data entry for nutritional interventions is often forgotten. As the feed rate given to a patient may be changed due to other clinical circumstances other than GC, it may be not updated within the STAR tablet. As evidenced by the consistently negative PN intervention differences, implying that the STAR tablet was not updated about the nutrition intervention change.

All of these are valid reasons for the low EN compliance, and could contribute to the higher non-compliance seen in EN interventions. In addition, the lower, lower quartile PN compliance may be due to PN interventions requiring a clinician to enter this information into STAR, rather than STAR prompting the clinician about its value. Hence, making data entry of PN more easily forgotten.

As the BG and insulin data entry compliance was relatively high, and the measurement discrepancies when non-compliant were very low (median BG measure +0.2 mmol/L on STAR and median insulin dose +500 mU/min on STAR, Table 6.2), non-compliance is likely due to accidental data entry error by the clinician. The differences in BG values entered are not large enough to imply purposeful modification of the resulting recommendation offered by STAR. In addition, as the insulin dose non-compliance differences are commonly only different by 0.5 U and/or 16.67 mU/min (1 U/hr infusion), implying accidental data entry error or STAR not being notified about the starting or stopping of a 1 U/hr insulin infusion. Thus, the slight reduction in both the BG and Insulin data entry compliance is most likely due to accidental data entry error by the clinician and STAR not being updated about insulin infusion changes.

It should be noted, if information is entered incorrectly into the STAR tablet it will result in the identified patient-specific $S_I$ to be either higher or lower than its actual value. Resulting in the recommendation given by STAR being either too aggressive or conservative. Thus, directly effecting GC performance. However, as STAR recommends interventions based on a 90% confidence interval the impact of incorrect data entry is minimised, as seen by the GC results in Table 6.1.

### 6.4.2 Recommendation compliance

The compliance of clinical staff following STAR's recommendations was extremely high, with approximately 100% of interventions followed in both cohorts (Table 6.3). In addition, given the total number of measurements and the total number of recommendation changes, a recommendation change is a very rare occurrence, occurring approximately once every 43-56 measurements. Thus, showing the strong compliance, and, as a result, trust of the STAR protocol.

Again, a minor discrepancy in the nutrition interventions was seen in the IQR in Table 6.3, consistent with the previous observations of data entry compliance. In addition, EN recommendations had the highest numbers of non-compliant cases in both cohorts (120 and 37, Table 6.3), emphasising the non-compliance of STAR's feed recommendations. The discrepancies in nutrition recommendations were consistently negative, suggesting that clinicians would consistently increase the nutrition interventions from what STAR recommended by approximately 20 mL/hr Table 6.3, emphasising point 2 of the reasons discussed in the previous section. However, these discrepancies could be due to all of the reasons discussed in the previous section. Equally, nutrition interventions are the most likely of the GC interventions to be altered by clinical circumstances, due to factors such as medical imaging, surgery, gastric tolerances etc. Therefore, making this discrepancy in the nutrition interventions less significant.

The number of non-compliant cases for both insulin bolus and infusion recommendations was very small in both cohorts. However, when an insulin intervention was changed, it was commonly to decrease the insulin bolus given by 1.0 U or increase the insulin infusion by 1.0 U/hr. This suggests that both less and more aggressive interventions were desired from the clinicians. However, the IQR of differences in Table 6.3, implies this is not consistent in all non-compliant insulin interventions. Overall, showing that the insulin interventions recommendations of STAR offer a good balance aggressive and safe GC.

### 6.4.3 Limitations

This analysis assumes all the data recorded on the bedside sheets is correct. In addition, any absence of data on the bedside sheet was assumed to be zero. However, from assessing trends in recorded insulin and nutrition data this assumption may be incorrect. In particular, the bedside sheet nutrition data (both enteral and parenteral) occasionally had a delay (1-2 hours) in the value being recorded by the STAR tablet, thus appearing as poor data entry compliance in this analysis. This may be due to the clinical staff not immediately updating STAR when the feed is stopped or started due to clinical circumstances. As a result, this may be one of the reasons for the poorer nutrition intervention compliance seen in Table 6.2.

The STAR sub-cohort only gives an approximate representation of the entire STAR Christchurch cohort, having similar demographic statistics of Age, Gender, ICU Length of stay and APACHE II Score (Table 6.1). However, there is a significant discrepancy in both ICU and Hospital mortality ($P = 0.04$, Table 6.1), although, this should not effect the compliance to the STAR protocol. In addition, the GC achieved and recommendation compliance in both cohorts was similar, both spending approximately 89% of time in the targeted 4.4-8.0 mmol/L band ($P = 0.89$, Table 6.1), and having almost identical recommendation compliance statistics. These results suggest the sub-cohort is a representative sample of the entire STAR cohort in terms of protocol compliance, and that future studies could use a similar, smaller group.

Overall, the high compliance seen by the STAR protocol suggests it is clinically practical and implementable, with enough flexibility to handle unexpected clinical circumstances and workload. This result suggests that the GC performance achieved by STAR seen in Chapter 5 *Clinical performance review of the STAR Glycaemic Control protocol*, is a function of the GC protocol and not the clinical staff involved. In addition, this analysis has shown that STAR's clinical usability may be improved by adjusting the nutrition intervention protocol and tablet recording.

## 6.5 Summary

This chapter investigated the compliance of the STAR GC protocol in terms of data entry and following STAR's recommendations. The information recorded by the STAR tablet was compared to bedside sheet information and STAR's recommendations. Data entry compliance was very high, with all intervention having over 86% of data entered correctly. Recommendation compliance was approximately 100%, with 1 in every 43-56 recommendations being changed, largely due to nutrition recommendation changes. In both the data entry and and recommendation compliance, the nutrition interventions (EN and PN) compliance was consistently lower than other interventions. This gap is likely due to either to the difficulty associated with changing the feed rate or clinical circumstances changing the feed rate and STAR not being updated.

This analysis supports the argument that STAR is a safe and effective GC protocol which clinical staff trust, and is flexible enough for the clinical environment to allow for very high compliance. However, it also shows that there is a slight room for improvement in terms of the way in which nutrition interventions are handled. Further investigation to the benefits of variable nutrition and potential simplification should be investigated.

# Chapter 7

# Clinical nutrition delivery of STAR

## 7.1 Background

The STAR GC protocol is unique in maintaining normal BG levels by changing both insulin and nutrition interventions [128], [147]. Changing nutrition interventions differentiates STAR all from other ICU GC protocols, which only change insulin interventions (e.g. [109], [126], [129], [214], [277]). STAR maximises nutrition in the context of GC to the targeted 4.4-8.0 mmol/L BG range [128], [147]. Hence, the level of nutrition it provides is a patient-specific, time-varying estimate of the ability to take-up glucose, and is only reduced in the face of significant insulin resistance.

Currently, there is also significant debate over the appropriate amount to feed an ICU patient. Many studies have shown mixed results in reviewing caloric intake, route, and timing, and their relation to outcome [100], [131], [134]–[136], [278]–[284]. Cahill et al. [263] surveyed the overall nutrition performance of 158 ICUs, from 20 countries, finding significant variation in nutrition delivery. This study also found the largest improvement for mortality outcomes to be at 85% of the caloric goal nutrition rate set by the respective ICU [135].

[1]**Stewart KW**, Chase JG, Pretty CG, Shaw GM. Nutrition delivery of a model-based ICU glycaemic control system. Ann. Intensive Care. 2018;8:4.**Stewart KW**, Chase JG, Pretty CG, Shaw GM. Nutrition delivery of a model-based ICU glycaemic control system. Ann. Intensive Care. 2018;8:4.

This ideal value, and the best performing unit surveyed, are used in this chapter as benchmarks for assessing the clinical performance of STAR's nutrition delivery.

This chapter first evaluates STAR's clinical provision of nutrition, to a cohort of hyperglycaemic ICU patients, compared to reports including all ICU patients in other ICUs from the survey of [263]. This comparison assesses if safe, effective GC precludes or limits high nutrition delivery, as well as determining if nutrition restriction to obtain effective GC limits total nutritional intake. Second, the inter- and intra- patient variation of nutritional delivery, while maintaining normo-glycaemia, is assessed to evaluate the range of glucose/nutrition tolerance in ICU patients on GC. Third, the relationship between morbidity and mortality, and nutrition delivery is retrospectively assessed to determine if nutrition restriction from GC affects outcome. The main outcomes assess, at a cohort level, the nutrition clinically provided by using STAR, in an international context, and whether or not a *'best'* nutrition rate is patient-specific, when considering patients requiring GC.

## 7.2 Methods

### 7.2.1 STAR GC Protocol

#### *7.2.1.1 GC Protocol Overview*

STAR modifies nutrition rate depending on the bounds of predicted potential behaviour, with a preference to increase insulin before reducing nutrition, and to raise nutrition whenever possible [128], [147]. Full details of protocol methodology can be seen in Section 1.2.4 *Stochastic Targeted (STAR) Glycaemic Control*. STAR modulates this nutrition rate between 30-100% of the caloric goal, with a maximum step change of ±30% of caloric goal per hour [128]. ACCP guidelines are used to determine patient-specific daily caloric goal based on 25 kcal/kg/day [156].

Overall, STAR attempts to provide the maximum nutrition rate a patient can tolerate, while keeping BG in the targeted 4.4-8.0 mmol/L range. However, in some patients, insulin saturation limits the ability of insulin to lower BG on its own [285]–[287], thus requiring nutrition restriction to assist in the lowering of BG. If the provision of excess carbohydrates, above this saturation limit, results in excess BG, the nutrition rate achieved by STAR represents an *'ideal'* patient-specific nutrition rate that does not result in hyperglycaemia, based on their current ability to tolerate glucose. It is thus a surrogate for a patient, and time specific maximum tolerable feed in the context of safe and effective GC.

#### *7.2.1.2 Christchurch Clinical Implementation*

Clinical data from 221 hyperglycaemic ICU patients treated with STAR (2011-2015) [215] in the Christchurch Hospital ICU (mixed medical ICU) was used to assess the performance of its variable nutrition delivery. BG, insulin and nutrition data is automatically collected by the STAR tablets when patients are on GC. The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of the retrospective data. Cohort demographics are given in Table 7.1.

Table 7.1: STAR cohort patient demographics and GC performance statistics

| *Patient Demographics* | |
|---|---|
| Number of Patients | 221 |
| Number Hours of GC | 21,769 |
| Age | 64.0 [54.0 - 72.0] |
| Sex (% Male) | 66.1 |
| ICU length of stay (Days) | 8.4 [3.1 - 15.3] |
| Days on GC | 2.67 [1.50 - 5.67] |
| Admission to GC Start (Hours) | 17.5 [7.3 – 53.8] |
| Operative (%) | 29.0 |
| APACHE II Score | 21.0 [16.0 - 27.0] |
| ICU Mortality (%) | 28.0 |
| *GC Performance Statistics* | |
| BG mean per-patient | 6.66 [6.36 - 7.21] |
| BG SD per-patient | 1.17 [0.85 - 1.65] |
| % time BG 4.4-8.0 mmol/L, per-patient | 88.42 [77.42 - 94.44] |
| % time BG 4.4-8.0 mmol/L, cohort | 83.2 |
| % time BG <4.4 mmol/L, cohort | 1.35 |
| # Patients <2.2 mmol/L | 4 |

*Acute Physiology And Chronic Health Evaluation (APACHE), Glycemic Control (GC), blood glucose (BG), standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

STAR has proven to provide excellent GC in this cohort, spending over 88% time, per-patient, in the targeted 4.4-8.0 mmol/L range, Table 7.1. STAR patients in Christchurch are typically fed enterally with low carbohydrate Glucerna$^{TM}$ Select (74.6 g/L Carbohydrate, 50 g/L Protein, 21.1 g/L Fibre, Abbott Labs, Illinois, USA), where these carbohydrate concentrations exclude indigestible fibre. PN is used occasionally, at clinicians discretion, to supplement EN. While STAR knows the PN value, it does not regulate it, enabling the possibility of nutrition delivery over 100% of the caloric goal.

Patients are not weighed in the Christchurch ICU so ACCP caloric goal feed is approximated by first estimating the patient weight. This estimation first assumes an 80 kg individual, and then modifies this value based on frame size (subjective assessment; small, medium, large), age and sex. The process uses Table 7.2 and Eq. (7.1) [112].

Table 7.2: Coefficients used to determine an ICU patient's estimated weight in Christchurch Hospital ICU.

| Frame Size (F) | Small | Medium | Large | |
|---|---|---|---|---|
| | 0.9 | 1.0 | 1.1 | |
| Age (A) | ≤39 | 40-59 | 60-79 | ≥80 |
| | 1.1 | 1.0 | 0.9 | 0.8 |
| Gender (G) | Male | | Female | |
| | 1.0 | | 0.8 | |

$$A \times F \times G \times 80 = \textit{estimated weight kg} \tag{7.1}$$

Eq. (7.1) modifies the estimated weight of 80 kg into a maximum range of 46.1-96.8 kg. In this cohort, the median and IQR of estimated weight was 72.0 [64.3 - 79.7] kg. This value is multiplied by the 25 kcal/kg/day ACCP caloric goal to find the patient's daily caloric goal. Due to clinical circumstances a patient's nutrition may be stopped or reduced significantly, for short periods, not reflective of the STAR feeding algorithm. Therefore, in this analysis, all occurrences of feeding less than the minimum specified by STAR, which is 30% of caloric goal, are ignored (3,135 hours, 14.4% of the time).

### 7.2.2 Analysis

#### *7.2.2.1 Overall Clinical Performance of STAR Nutrition Protocol*

The mean cohort caloric goal achieved per day in the ICU by STAR, considering only hyperglycaemic ICU patients on STAR, is calculated and compared to the entire ICU patient cohorts reviewed by Cahill et al. [263]. For STAR, information only exists for periods of GC, which are aligned to the appropriate day of ICU stay to ensure that comparisons to Cahill et al. [263] are valid. Note, as

data was only taken from the STAR tablet, this may not be what was actually given/recorded on the bedside sheet. However, the analysis in Chapter 6 *Compliance of the STAR Glycaemic Control Protocol* shows the STAR records to be largely representative of the bedside sheet information. This comparison helps answer whether caloric restriction to obtain safe and effective GC, or if safe, effective GC in general, preclude or limit nutrition delivery when compared to that achieved by an entire ICU patient cohort.

#### *7.2.2.2 Per-patient Clinical Performance of STAR Nutrition Protocol*

The distribution, per-patient (median, IQR, 5th – 95th range), of caloric goal achieved per day on STAR is calculated. The per-day distribution is compared to the best performing ICU surveyed in [263] and the 85% optimum caloric goal of [135] to evaluate the percentage of patients who can tolerate more, or less, nutrition than these levels. This comparison delineates the range and distribution of glucose and nutrition tolerance for these mixed medical ICU patients, and assesses how well STAR performs, per-patient, compared to other ICUs and a *'best'* level, with respect to outcome.

The mean and SD of caloric goal achieved over a patient's entire stay is assessed in terms of median and IQR between patients, and to the overall variation seen per day across the entire cohort. This analysis assesses if the overall variability seen per day is due to variable patients or different and variable patient and time specific tolerance of nutritional uptake.

The relationship between mortality and morbidity, and caloric goal achieved, is also investigated in relation to the optimum caloric goal of 85% goal feed presented in [135]. This analysis assesses whether glucose restriction to obtain GC, due to limited patient-specific glucose tolerance, is associated with increased morbidity and mortality. The outcome may also delineate a potential limit in this regard.

## 7.3 Results

### 7.3.1 Overall Clinical Performance of STAR Nutrition Protocol

The percentage caloric goal clinically achieved by STAR, each day in ICU, was compared to the survey results in Cahill et al. [263]. Fig. 7.1 shows the mean nutrition delivered to hyperglycaemic ICU patients by the STAR nutrition protocol performs very well compared to all ICU patients in the best performing ICU reviewed in Cahill et al., only slightly under-performing after day 3. It is well above the mean ICU surveyed in [263] on all days. In addition, the mean percentage caloric goal nutrition exceeds the ideal 85% caloric goal [135] from day 4 onwards, and is within 5% after day 1.

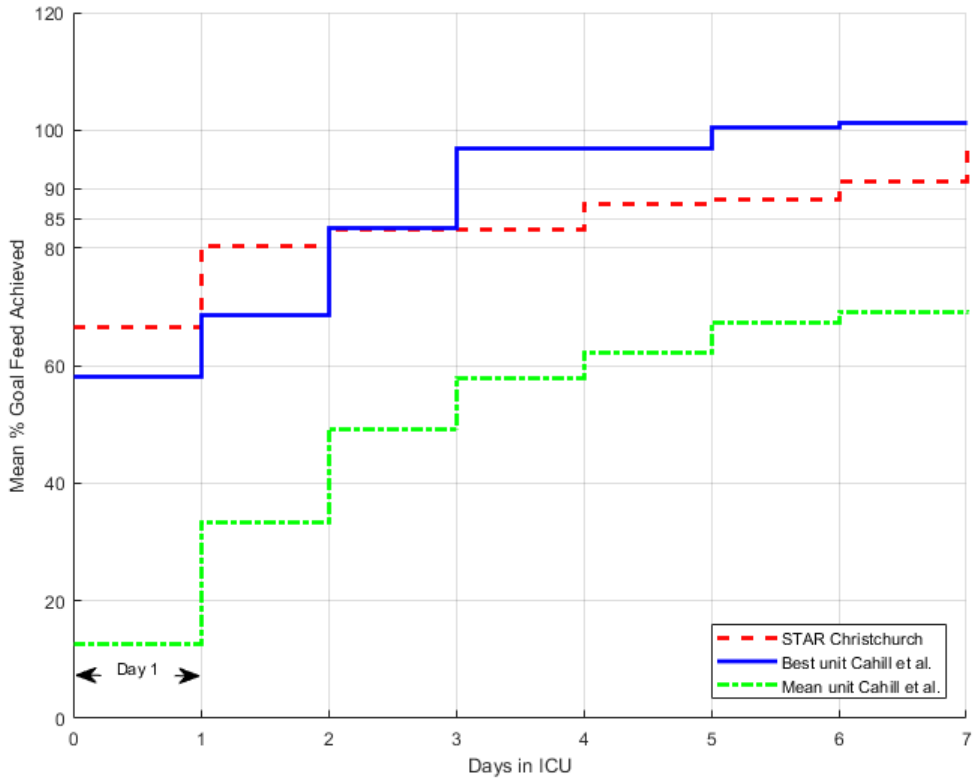



Figure 7.1: Comparison of mean percentage caloric goal achieved for each day in the ICU between the clinical STAR Christchurch results and the results published in Cahill et al. [263]. The ideal 85% caloric goal, to minimise mortality, presented in Heyland et al. [135] is also indicated for comparison.

### 7.3.2 Per-patient Clinical Performance of STAR Nutrition Protocol

Fig. 7.2 shows the distribution of per-patient mean caloric goal achieved per day by STAR, including IQR and 5th – 95th percentile values. It clearly shows large variation in patient-specific nutrition rates on the first day of ICU stay, which narrows as patient-specific metabolic state stabilises [122]. Over 56.2% of patients reach or exceed the ideal 85% caloric goal in [135] after day 2, reaching 73.5% on day 7. The percentage of patients over the mean ICU result in [263] are also shown ranging from 100% on day 1 to 85.7% on day 7. Overall, in comparison to Fig. 7.1, the per-patient results clearly show some patients cannot achieve this cohort mean rate or the ideal 100% caloric goal.

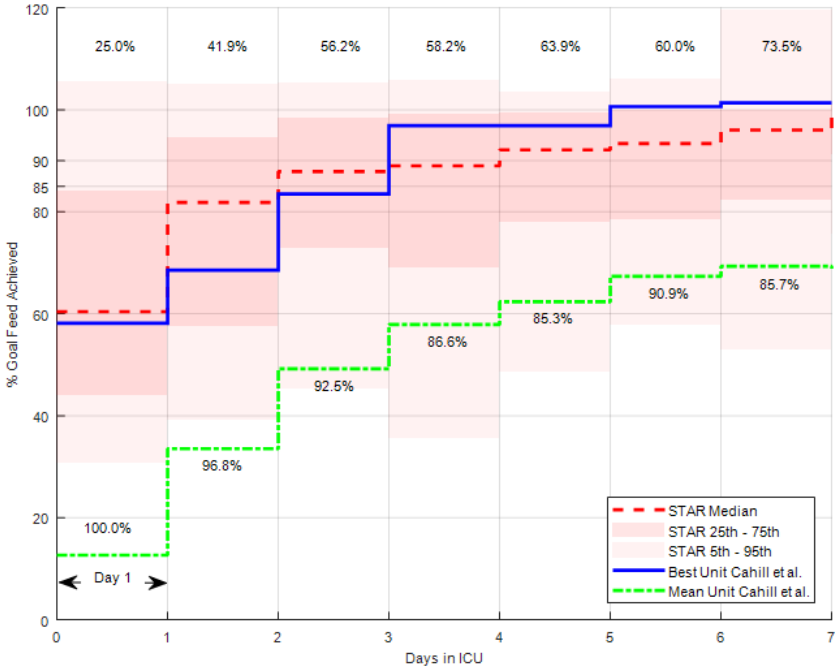



Figure 7.2: Comparison of STAR Christchurch's percentage caloric goal distribution achieved clinically (N = 221 Patients) and the best, and mean performing unit reviewed in Cahill et al. [263]. The percentage of patients per day $\geq$ the mean of the units surveyed in in Cahill et al. [263] is provided for comparison (Above mean unit trace). The ideal 85% caloric goal, to minimise mortality, presented in Heyland et al. [135] is also indicated for comparison in conjunction with the percentage of patients per day $\geq$ 85% caloric goal (Along top of figure).

As noted, the rates in Fig. 7.2 are an estimate of the *'ideal'* time-varying patient-specific nutrition uptake in the context of GC to the targeted 4.4-8.0 mmol/L BG range. Equally, some variability is due to patients starting or finishing GC. Hence, the results of Fig. 7.2 are a conservative or worst-case analysis.

Table 7.3 shows the median of the mean per-patient feed rates achieved is relatively high at 89.8% caloric goal, but has a large IQR of 23.9% ([74.3 - 98.2]). However, the relatively small median of the per-patient feed rate SD, over a patient's stay, of 12.9% shows individual patients are less variable than the cohort. Thus, the overall ability to tolerate glucose is patient-specific. Therefore, it is clear the ability to take up, and thus to deliver, nutrition varies significantly between GC patients.

Table 7.3: Per-patient feed rate characteristics.

| | |
|---|---|
| Number of Patients | 221 |
| Mean caloric goal achieved over entire stay (%) | 89.8 [74.3 - 98.2] |
| SD of caloric goal achieved over entire stay (%) | 12.9 [4.6 - 20.4] |

*standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

The relationship between mean percentage caloric goal achieved over a patient's entire stay and APACHE II Score, and ICU mortality are shown in Fig. 7.3. Both figures show the mean feed rate achieved appears unrelated to APACHE II Score and ICU mortality (P = 0.68). In addition, logistic regression suggests the probability of mortality, given the mean percentage caloric goal achieved, might not differ statistically from a constant model. This data suggests STAR feeds all patients *'equally'*, independent of morbidity or mortality, and thus the patient-specific ability to tolerate glucose is not associated with APACHE II Score or ICU mortality in this mixed medical ICU cohort. Alternatively, the low number of feed rates below the mean ICU in [263] may indicate that the nutrition rates obtained are well above any clear limit to show a trend in morbidity or mortality.

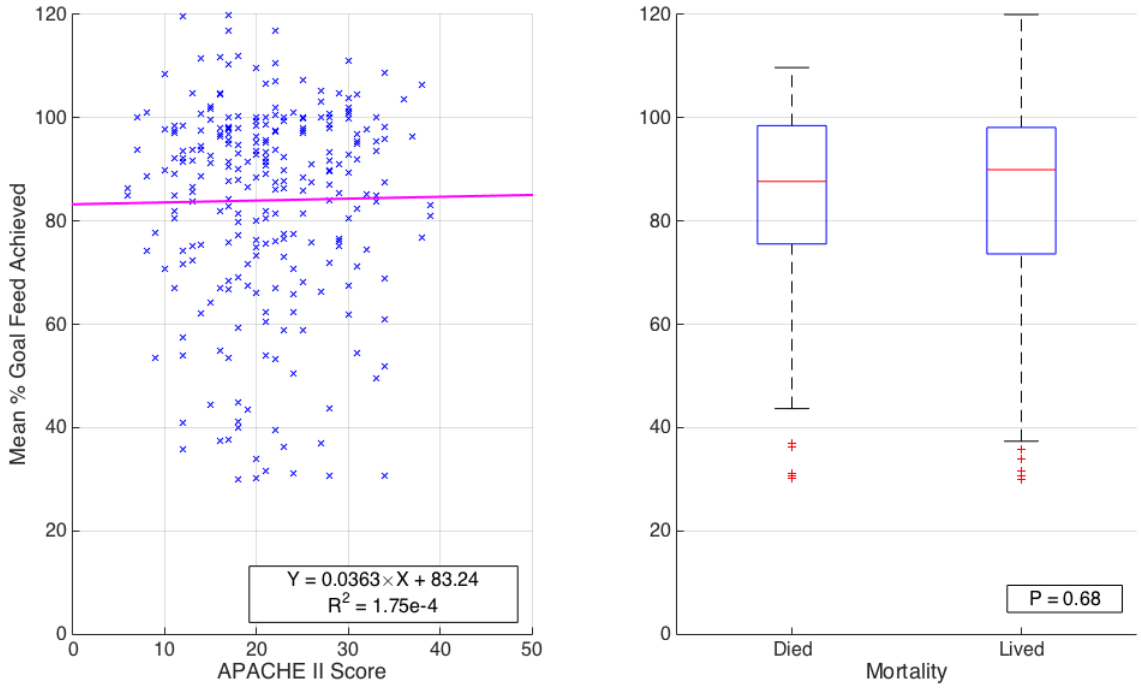



Figure 7.3: Left Panel: Comparison of mean percentage caloric goal achieved vs Acute Physiology And Chronic Health Evaluation (APACHE) II Score. Logistic regression results shown in bottom right corner. Right Panel: Comparison of mean percentage caloric goal achieved vs ICU mortality. P-value shown in the bottom right corner to show significance of relationship.

## 7.4 Discussion

### 7.4.1 Overall Clinical Performance of STAR Nutrition Protocol

Fig. 7.1 shows STAR's nutrition protocol, on hyperglycaemic ICU patients, performs equal to or better than, the average of all the ICU patients in the best ICU surveyed by Cahill et al. [263] over the first 3 days of ICU stay. After day 3, the best ICU performs slightly better. However, as seen in Table 7.1, the median patient spends 2.67 days on protocol and starts GC within 17.5 hours of ICU admission, indicating the majority of patients are finished GC after ICU day 3. This outcome makes the relevance of nutrition performance less significant after this time.

Overall, these outcomes show the current STAR nutrition protocol delivers clinical nutrition, for hyperglycaemic patients, equal to, or better than, those reported in the Cahill et al. survey for all ICU patients in 158 ICUs from 20 countries [263]. It is clear that high nutritional delivery and safe, effective GC are not mutually exclusive. Therefore, STAR's modulation of nutrition to achieve GC does not reduce total nutrition intake when compared to an entire ICU cohort.

### 7.4.2 Per-patient Clinical Performance of STAR Nutrition Protocol

Fig. 7.2 shows a large variation in nutrition rates achieved per day, per-patient, narrowing and rising as the patient-specific metabolic state stabilises [122]. However, the median variation per-patient was only 12.9 [4.6 - 20.4] % (Table 7.3), suggesting patients do not deviate significantly from their mean nutrition rate. This result and the large IQR of the mean feed rates achieved (74.3% - 98.2%, Table 7.3) suggest the lower nutritional delivery to the 5th and 25th percentile are a result of a few patients who had a lower ability to tolerate glucose intake.

Considering STAR feeds the maximum possible nutrition, while maintaining normo-glycaemia, the nutrition rates achieved give a good indication of the patient-specific ability to tolerate glucose and thus their *'ideal'* nutrition rate. In essence, every patient is fed the maximum they can achieve with added insulin. Therefore, the spread of nutrition rates per-patient in Fig. 7.2 infer this *'ideal'* nutrition rate is very patient-specific, and evolves with time.

This maximum/*'ideal'* nutrition rate achieved by STAR was less than the 100% caloric goal for more than 50% of patients, over all days. In addition, the best unit surveyed in Cahill et al. [263] was still considerably lower than their predetermined caloric goal, suggesting these generalised approximations do not represent all ICU patients well, as seen in Fig. 7.2 for STAR in Christchurch.

Fig. 7.3 showed no apparent relationship between the nutrition delivered to hyperglycaemic ICU patients and either APACHE II Score or ICU mortality. A value of $P = 0.68$ suggests ICU mortality and mean percentage goal feed achieved on GC are not significantly different, contrary to the results seen in [100], [131], [135], [267], [282]. However, the number of patient's which died are low, and therefore we do not have enough power (38% t2 test) to assess the relationship between ICU mortality and mean percentage goal feed achieved. Equally, this is an unadjusted analysis and doesn't account for other known factors related to ICU mortality. However, of note, none of the studies which were assessing feed in relation to ICU mortality particularly considered GC or glycaemic levels.

In this study, glycaemia was well-controlled for virtually all patients to an intermediate BG band associated with improved outcomes [61], [142], where it has recently been shown that the patient-specific metabolic variability is independent of patient outcome [288]. In addition, over 56% of patients exceeded the lower 85% optimum of [135] by day 3. Thus, the lack of a trend in this data may be due to any number of factors including: very low numbers of patients who were *'underfed'* or in the lowest tertile of goal feed, the impact of GC and outcome glycaemia not considered in other analyses, and/or other factors.

In addition, the median duration on STAR was 2.67 days, while the relationship presented in Heyland et al. [135] is over the first 12 days in the ICU, and it considered all days of stay whereas this study only has data for days on GC. This difference is a possible study limitation. However, after STAR GC, when patients are stable enough to stop GC (>5 hours in target BG band), nutrition rates remain the same or rise, so this result is likely to still hold. Overall, these results suggest the, generally high, nutrition rates achieved by STAR were independent of morbidity and mortality, although there was no clear lower limit or optimal value.

The STAR GC protocol, uses model-based, patient-specific control in conjunction with a stochastic model to predict the best treatment for a patient. As shown by Table 7.1 and Chapters 5 and 6, STAR is able to achieve very good GC with a compliance of over 86.5% in all interventions and near identical results across multiple ICUs [215]. However, in many clinical practices, the idea of protocol-driven changes in the nutrition given to a patient for GC is foreign, and thus clinically unacceptable. Thus, the main focus of this study is to show that protocol-driven changes in nutrition rate do not preclude achieving better nutrition delivery rates than those of 158 ICUs from 20 different countries. This study shows that high nutrition delivery and safe, effective GC are not exclusive. Equally, these results show nutrition restriction to obtain GC does not necessarily reduce total nutrition intake in an international context. Hence, nutrition restriction for GC should be considered more directly as a part of GC protocols.

### 7.4.3 Limitations

Cahill et al. [263] provides the percentage caloric goal nutrition achieved by each ICU. However, caloric goals may vary across ICUs. As a result, some ICUs may achieve caloric goal nutrition targets *'more easily'* than others, making comparison difficult. Additionally, the estimation of a patient's body weight used by the Christchurch ICU [112], Table 7.2 and Eq. (7.1), may also bias the caloric goal feed estimated for a patient. However, the 25 kcal/kg/day ACCP guideline [156] used in the Christchurch ICU, or a similar value guideline (25-30 kcal/kg/day SCCM/ASPEN [289], and 20-25 kcal/kgBW/day initial phase and recovery phase 25-30 kcal/kgBW/day ESPEN [290]), is commonly used, and these cover the range used with STAR patients.

The mean nutrition rate achieved by the best unit surveyed by Cahill et al. [263] was still considerably lower than the predetermined ACCP caloric goal over the first 3 days, suggesting these generalised approximations do not represent all patients well, as seen in Fig. 7.2. This reduction is likely due to patients being unable to tolerate the 100% feeding, resulting in high gastric residuals and other negative effects. In addition, the patient-specific nutrition rates presented in Fig. 7.2 are dependent on the carbohydrate content of the feed type given. Hence, considering that the nutrition rate is in relation to a patient's glucose tolerance, and the glucose content of feed types used vary across

ICUs, the percentage caloric goal a cohort can tolerate is likely ICU specific. However, this value could be easily changed to be in terms of only glucose concentration to allow better integration into other ICUs, with varying feed types.

Moreover, Cahill et al. surveys the nutrition given to *'all'* ICU patients, where this study only considers patients who required GC. The approximately 25-35% of patients who require GC in the ICU [107] are the most metabolically stressed, and, as a result, have reduced glucose uptake capacity. They are thus often harder to deliver the target nutrition rates [280], [291]. Therefore, providing excellent GC and achieving nutrition rates similar to that achieved for all ICU patients, normo-glycaemic and hyperglycaemic, in the best ICU reviewed in [263] is a significant outcome.

Other factors, such as mechanical ventilation, neurologic injury, gastric emptying, and paresis patients are well known to influence the nutritional requirements of ICU patients. This study is only a retrospective analysis, for which this detailed information is not available, and thus cannot be accounted for. However, the cohort was typical of a mixed medical ICU.

## 7.5 Summary

The STAR GC protocol clinical provision of nutrition to hyperglycaemic patients was compared to nutrition rates of entire ICU cohorts surveyed in 158 ICUs in Cahill et al. [263]. Mean nutrition rates clinically achieved by the STAR nutrition protocol were significantly higher than the mean and best ICU surveyed, for the first 3 days of ICU stay. Overall, STAR's protocol-driven changes in nutrition rate provide on average nutrition rates for hyperglycaemic patients which are equal to, or better than, the mean of all ICU patients in 158 ICUs from 20 different countries. More importantly, these outcomes show high nutrition delivery and safe, effective GC are not mutually exclusive, and that restricting nutrition for GC does not limit overall nutritional intake when compared to other ICUs.

The inter- and intra- patient variation of nutritional delivery was assessed in the STAR cohort. There was large inter-patient variation in nutrition rates achieved per day, which reduced overtime as patient-specific metabolic state stabilised. Median intra-patient variation was 12.9%, however the IQR of the mean per-patient nutrition rates achieved was 74.3% - 98.2%, suggesting patients do not deviate much from their mean patient-specific nutrition rate and the ability to tolerate glucose intake varies significantly between, rather than within, patients. There is significant inter-patient variability between patients to tolerate and uptake glucose, where intra-patient variability over stay is much lower. Therefore, a best nutrition rate is likely patient-specific for patients requiring GC.

The relationship between mean nutrition rate achieved and morbidity, and mortality was investigated. The nutrition rates delivered by STAR showed no association between nutrition delivery to hyperglycaemic patients and morbidity or mortality. This result/outcome may have been due to no or very few *'underfed'* patients or the patients receiving safe and effective GC. Overall, these results suggest the generally high nutrition rates achieved by STAR were independent of morbidity and mortality, although there was no clear lower limit or optimal value.

From the results seen in Chapter 6 *Compliance of the STAR Glycaemic Control Protocol* and this chapter it can be inferred the slightly poorer nutrition intervention compliance should not

be the result of STAR feeding too low, but rather the frequency of feed changes. Therefore, further investigation into the simplification of the STAR feeding protocol should be undertaken to improve STAR's nutrition intervention compliance. This chapter's analysis provides a good basis and reference for what is currently achieved with the current variable STAR feeding protocol.

# Chapter 8

# Simpler STAR nutrition protocols

## 8.1 Background

The STAR GC protocol is unique in maintaining normal BG levels by changing both insulin and nutrition interventions [128], [147]. Changing nutrition interventions differentiates STAR all from other ICU GC protocols, which only change insulin interventions [108], [109], [126], [129], [214], [268], [277]. However, the clinical workload and complexity of GC may be increased due to the nutrition changes required by STAR, in turn affecting compliance and control quality for some ICUs, as discussed in Chapter 6 *Compliance of the STAR Glycaemic Control Protocol* [101], [151], [272]. Thus, simplifying the STAR nutrition protocol, while maintaining its safe and effective GC, could decrease clinical workload and complexity, and increase its clinical suitability.

Currently, there is also significant debate over the appropriate amount to feed an ICU patient. Many studies have shown mixed results in reviewing caloric intake, route, and timing, and their relation to outcome [100], [131], [134]–[136], [278]–[284]. Cahill et al. [263] surveyed the nutrition performance

[1]**Stewart, K. W.** , Chase, J. G., Pretty, C. G., and Shaw, G. M. (2017) 'Nutrition delivery, workload and performance in a model-based ICU glycaemic control system', Computer Methods and Programs in Biomedicine. (Under Review)

[2]**K. W. Stewart**, C. Pretty, J. G. Chase, and G. M. Shaw, "The Effect of Variable vs Fixed Feeding on Glycaemic Control in the Adult ICU: Virtual Trial Evaluation," in 20th World Congress The International Federation of Automatic Control, 2017.

[3]**K. W. Stewart**, J. G. Chase, J. Dickson, C. Pretty, and G. Shaw, "Can we fix it? Yes we can! Simplifying nutrition in STAR Glycemic Control.," in 16th Annual Diabetes Technology Meeting, 2016.

of 158 ICUs, from 20 countries, finding significant variation in nutrition delivery. This study also found the ideal relation to improved mortality outcomes to be at 85% of the caloric goal nutrition rate set by the respective ICU [135]. This ideal value, and the best unit surveyed, are used in this chapter as benchmarks for assessing the alternative, reduced workload nutrition protocols for STAR.

This chapter evaluates three simpler, reduced workload, alternative nutrition protocols for STAR using clinically evaluated virtual trials [154], [230]. The results are then compared to the current nutrition protocol and the survey in [263]. Each protocol is assessed in terms of GC performance, safety and workload.

## 8.2 Methods

### 8.2.1 Current nutrition protocol

#### *8.2.1.1 STAR Variable nutrition*

STAR currently modifies the nutrition rate depending on the stochastic prediction bounds of potential patient behaviour, with a preference to modulate insulin before reducing nutrition, and to raise nutrition if possible [128], [147]. ACCP guidelines are used to estimate the patient's daily caloric goal [156]. STAR modulates nutrition rate between 30-100% of caloric goal, with a maximum step change of ±30% caloric goal per hour [128]. STAR attempts to provide the maximum nutrition rate a patient can tolerate, while keeping BG in the 4.4-8.0 mmol/L range. The complete GC protocol details can be seen in Section 1.2.4 *Stochastic Targeted (STAR) Glycaemic Control.* Thus, the nutrition rate achieved by STAR gives a good indication of the patient and time specific *'ideal'* nutrition rate that does not result in hyperglycaemia, in regard to their current ability to tolerate glucose, as discussed in Chapter 7 *Clinical nutrition delivery of STAR.*

STAR patients in the Christchurch Hospital, ICU are typically fed enterally with the low carbohydrate Glucerna$^{TM}$ Select (95.7 g/L Carbohydrate, 50 g/L Protein, 21.1 g/L Fibre, Abbott Labs, Illinois, USA), where these carbohydrate concentrations exclude indigestible fibre. PN is used occasionally, at the discretion of clinical staff, to supplement EN. STAR accounts for, but does not regulate, this added PN. This original nutrition protocol is referred to as the variable nutrition protocol.

This variable nutrition protocol changes nutrition rate every 1-2 interventions, significantly increasing total workload and the apparent protocol complexity [101], [151], [272]. In addition, varying nutrition, even if patient-specific, is also unusual in GC and ICU clinical practice in general. Hence, a fixed or semi-fixed approach could significantly reduce complexity and workload.

### 8.2.2 Alternative nutrition protocols

Three simpler, lower workload alternatives are investigated. All three protocols are set in terms of the percentage of ACCP caloric goal achieved [156], as in STAR currently. Their performance is

compared to the current variable nutrition STAR protocol using clinically evaluated virtual trials [154], [230]. Each alternative nutrition protocol is designed to reduce clinical workload by fixing nutrition rates for all patients, either for their entire stay or per day of stay, leaving STAR to only modulate insulin.

#### *8.2.2.1 Fixed nutrition rate*

As noted, most GC protocols do not change the nutrition rate a patient receives, at least not per protocol. As a result, nutrition rates are fixed, or relatively so, at the caloric goal set for that patient, with changes only being made ad-hoc by clinical staff. Therefore, a 100% caloric goal fixed nutrition protocol, Fig. 8.1, is investigated, even though it is not typically achieved in even the best performing ICUs [263].

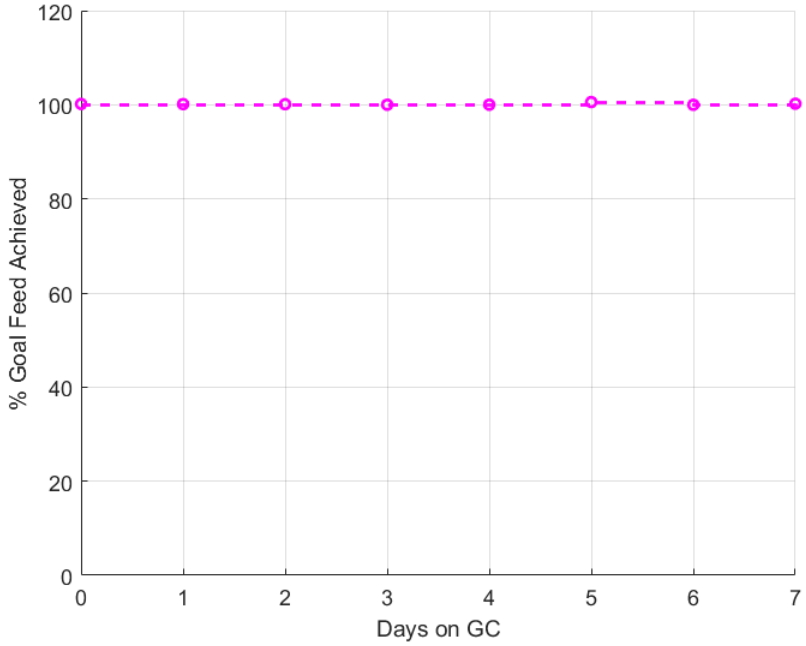



Figure 8.1: Fixed nutrition protocol.

#### *8.2.2.2 Stepped nutrition rates (by day)*

As an ICU patient is most stressed immediately post-surgery or traumatic event [73], they are the most likely to require GC at the beginning of their ICU stay [78], [85], [86]. In this study, 59.3% of patients started GC within 24 hours of being admitted to the ICU (Median 15.5 hours after admission, Table 8.1). In particular, prior studies have shown a patient's metabolic state ($S_I$) is lowest and most variable during their first 2-3 days of ICU stay [125], [228], [254], [288], [292], making GC more difficult and dynamic over this period.

If less nutrition is given to a patient over these first few days, less insulin is required to lower BG, and ultimately, the risk due to any potentially large variations in $S_I$ during this more volatile period are reduced. This reduction in nutrition thus enables safer, and more effective GC over this period. In addition, the median length of time on GC, for each STAR patient, is 2.2 days, Table 8.1. Thus, a stepped nutrition protocol, which varies nutrition by day over this period, will have the largest influence on the GC quality and safety.

ICU patient metabolism can vary significantly [122], [123], [292] and as a result, their nutritional uptake can also vary significantly, as seen in Fig. 8.3 and Chapter 7. Thus, any fixed/stepped nutrition protocol will result in some patients being *overfed* or *underfed*, relative to their ability to tolerate glucose. Although both of cases are not ideal, the consequences of each vary.

If patients are *overfed*, it may result in higher insulin doses being required to lower BG, emphasising any variability in the patient-specific metabolic state, $S_I$ [122], [123], [292]. Especially considering that $S_I$ is most variable over the first 3 days of ICU stay [122], [254], [288], [292]. Ultimately, *overfeeding* patients would increase insulin requirements, and thus BG variability, and the risk of hypoglycaemia, and, as a result, clinical workload to maintain patient safety. However, if patients were *underfed*, it would result in lower/no insulin doses being required to lower BG, and thus likely achieving safer, less variable, more effective, and more workload efficient GC, at the expense of potential complications due to not meeting nutritional requirements. Although, if not *underfed* substantially, these complications may not arise as shown by previous studies [134], [284], [293].

*Cahill et al. best (CB) [263] stepped nutrition rate:*

One goal of a stepped nutrition protocol could be to provide nutrition delivery equivalent to or better than the best unit surveyed by Cahill et al. [263]. Therefore, a stepped nutrition protocol of 60, 80 and 100% caloric goal, by day, over the first 3 days of GC, and 100% thereafter, is selected to match the beginning and the end of the best unit surveyed, over a 3 day period, Fig. 8.2. It thus *under feeds* most STAR patients, over the first 2 days, compared to the patient-specific variability shown in Fig. 8.3.

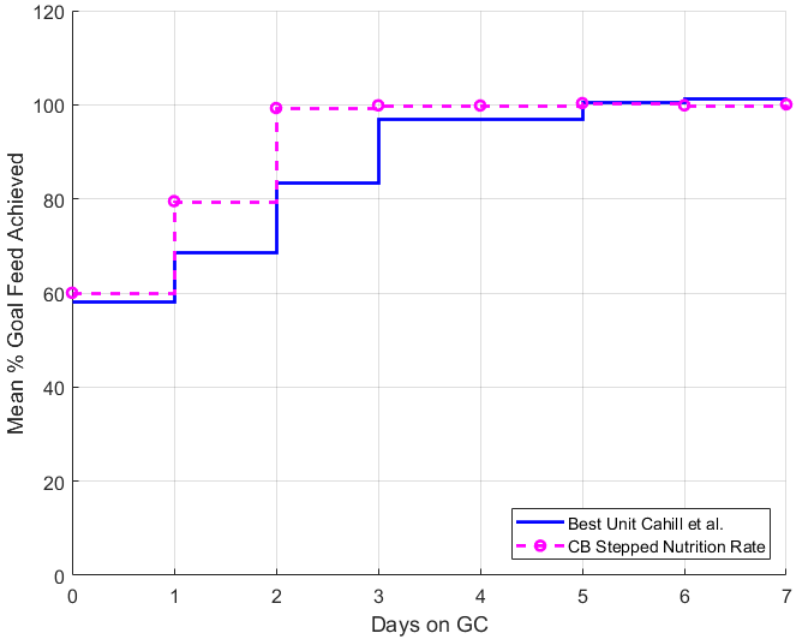



Figure 8.2: Cahill et al. best (CB) stepped nutrition protocol in comparison to the best performing unit surveyed in Cahill et al. [263].

*STAR lower quartile (SLQ) stepped nutrition rate:*

As noted, the nutrition rate achieved by STAR's variable nutrition protocol gives a good indication of the patient's *'ideal'* nutrition rate that doesn't result in hyperglycaemia, based on their current ability to tolerate glucose. Therefore, if patients were fed the lower quartile nutrition rate achieved clinically by the variable nutrition protocol, as shown in Fig. 8.3, 75% of patients would be fed less than what was achieved clinically with STAR. Hence, 75% of patients would be *underfed*, promoting further safety by lowering the required insulin doses. In addition, having a final fixed caloric goal

of 85% matches the minimum feed rate associated with the best mortality outcome, as reported in [135]. Therefore, a stepped nutrition protocol of 65, 75 and 85% caloric goal, by day, over the first 3 days of GC, and 85% thereafter, is selected based, Fig. 8.3.

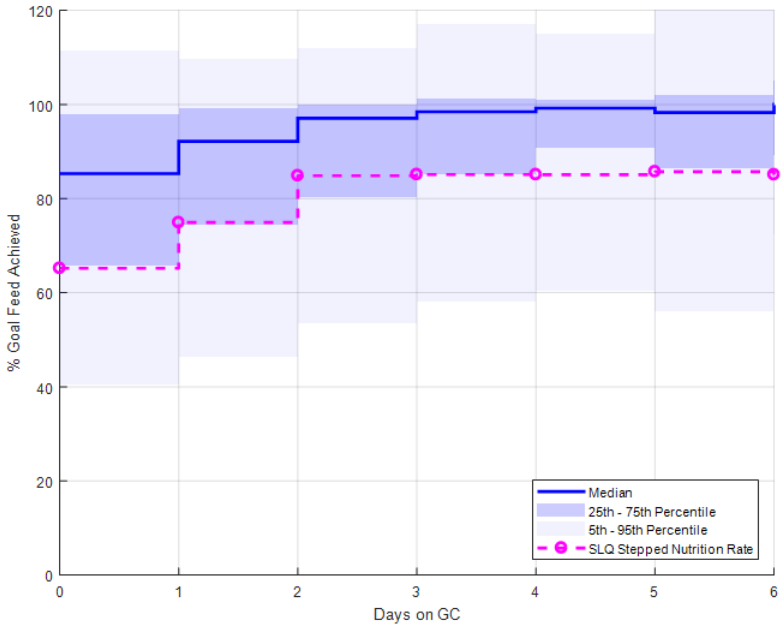



Figure 8.3: STAR lower quartile (SLQ) stepped nutrition protocol in comparison to the clinical results achieved by the STAR variable nutrition protocol.

Fig. 8.3 clearly shows large variation in nutrition rates achieved clinically, per-patient, on the first day of GC, which narrows as patient-specific metabolic state stabilises. Note, the nutrition rate may exceed the 100% caloric goal when extra clinical interventions are given, such as PN. Hence, as noted, the rates in Fig. 8.3 are an estimate of the *'ideal'* patient-specific nutrition uptake in the context of GC to the 4.4-8.0 mmol/L BG range, and a minimum value given.

### 8.2.3 Patient Data and Virtual Trials

Virtual patients are created by fitting the time varying model-based $S_I$ parameter to each patient's clinical data [154], [230], where model-based $S_I$ is a marker of patient-specific metabolic state [122], [294]. The $S_I$ profile is then used with a GC protocol, which specifies insulin and nutrition, to simulate the BG response [154], [230]. The clinically determined ACCP caloric goal and typically used Glucerna$^{TM}$ Select (Section 7.2.1.2) is used in each patient's GC simulation. Each of the

alternative STAR nutrition protocols is simulated on the virtual STAR cohort and their GC safety, performance and workload are assessed.

Clinical data from 221 patients treated with STAR (2011-2015) [215] in the Christchurch Hospital, ICU was used to create virtual patients. The cohort demographics are given in Table 8.1. The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data.

Table 8.1: STAR cohort patient demographics.

| | |
|---|---|
| Number of Patients | 221 |
| Number Hours | 21,1769 |
| Age | 64.0 [54.0 - 72.0] |
| Sex (% Male) | 66.1 |
| ICU length of stay (Days) | 8.4 [3.1 - 15.3] |
| Days on GC | 2.2 [1.2 - 3.9] |
| Admission to GC Start (Hours) | 15.5 [6.7 – 46.7] |
| Operative (%) | 29.0 |
| APACHE II Score | 21.0 [16.0 - 27.0] |
| ICU Mortality (%) | 28.0 |

*Intensive Care Unit (ICU), Glycemic Control (GC), Acute Physiology And Chronic Health Evaluation (APACHE). Data presented in Median [inter-quartile range (IQR)] where appropriate.

ACCP caloric goal of 25 kcal/kg/day [156] is used for all the nutrition protocols investigated. In the ICU the patient-specific caloric goals are recorded for all patients, and thus, are used as the patient-specific caloric goal in this study. For full details on the calculation of caloric goal in Christchurch Hospital ICU, NZ, see Section 7.2.1.2.

### 8.2.4 Analysis and statistics

Each of the proposed STAR nutrition protocols are assessed in terms of GC performance, safety, and workload. An analysis of the first 3 days of GC, in terms of performance and workload, is also performed to assess where the largest impact is achieved. The first 3 days are specifically chosen for assessment due to the median time on GC being 2.2 days, Table 8.1, and 67% of patients having finished GC by day 3. The metrics assessed comprise of:

**Performance:**
- Percentage of time in targeted BG band (4.4-8.0 mmol/L) [61], [142].
- Percentage of time hyperglycaemia occurs (BG $>$ 10 mmol/L).

**Safety:**
- Number of mild and severe hypoglycaemia patients (Number of patients with BG $<$ 4.0 mmol/L and BG $<$ 2.2 mmol/L, respectively) [35] [34].

**Workload:**
- Number of BG measurements per day, per-patient.
- Number of intervention changes (insulin and nutrition) per day, per-patient.
- Summed total of the number of intervention changes (insulin and nutrition rate changes) and BG measurements over the entire cohort.

Due to the irregular 1-3 hourly measurement intervals in STAR [128], [147], patient BG data was analysed with linear interpolation at 60 min intervals to enable fair comparisons [246], per Chapter 2 *Interpretation of Retrospective BG Measurements*. BG performance statistics are presented as median and IQR of the mean and SD of BG for individual patients per the consensus recommendations in Finfer et al. 2013 [137].

Non-parametric statistics are used exclusively due to the typically skewed distributions of BG, insulin dose and other data. P-values were computed using the Mann-Whitney rank-sum test for all continuous data and the chi-squared test for categorical data. P-values $<$0.016 are considered statistically significant after Bonferroni correction [224] for multiple comparisons.

## 8.3 Results

### 8.3.1 Nutrition protocol simulations

The three alternative nutrition protocols and the current variable nutrition protocol were simulated on the virtual STAR cohort. Fig. 8.4 compares the mean percentage of the caloric goal per day achieved in virtual trial simulation for each nutrition protocol to the best unit surveyed in Cahill et al. [263]. All three alternative nutrition protocols deliver more nutrition over the first 3 days of ICU stay than the best unit surveyed in Cahill et al. [263].

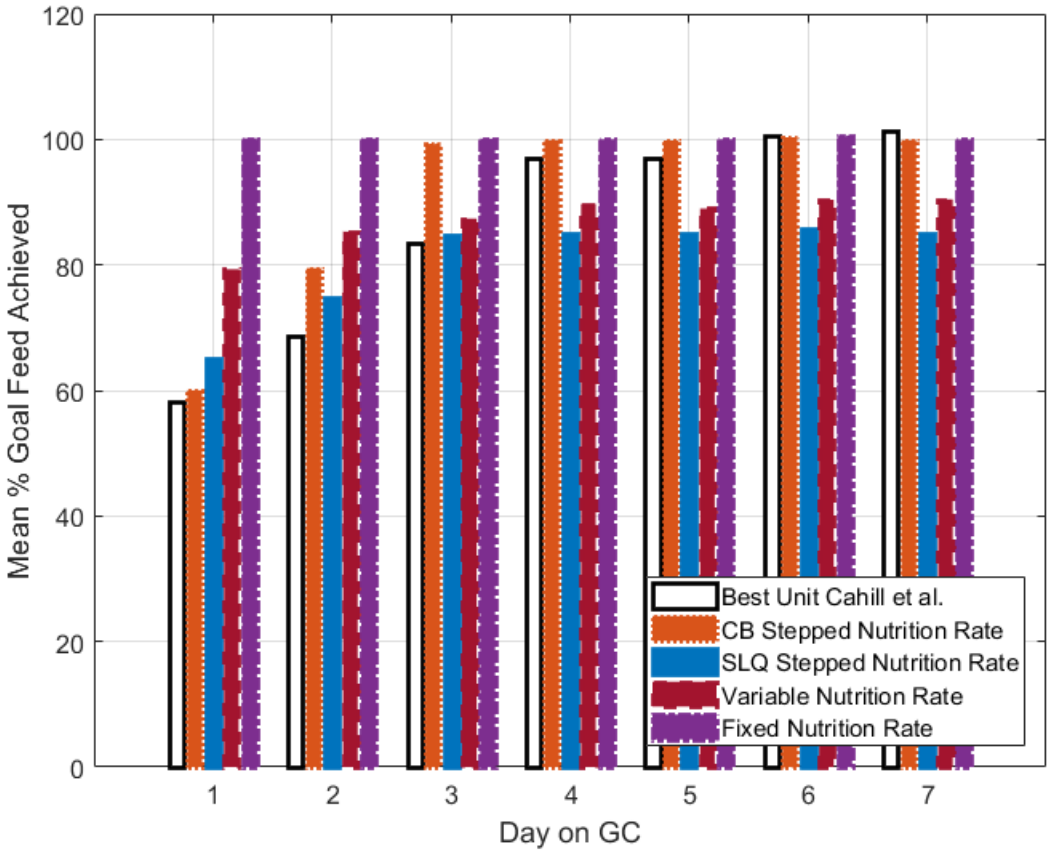



Figure 8.4: Comparison of mean percentage caloric goal achieved for each day on Glycemic Control (GC) between each of the simulated nutrition protocols (Variable, Fixed, Cahill et al. best (CB) stepped, and STAR lower quartile (SLQ) stepped) and the best unit surveyed in Cahill et al. [263]. These nutrition rates are fixed for all alternative nutrition protocols, for all patients.

### 8.3.2 Glycaemic performance and safety

The GC performance and safety for each simulated nutrition protocol is shown in Table 8.2. The current variable nutrition protocol and both stepped nutrition protocols had very similar GC performance, with very similar percentages of time in the targeted 4.4-8.0 mmol/L BG band (89.0% Var. vs. 88.3% CB and 89.5% SLQ, P=0.88 and P=0.64 respectively). In contrast, the fixed nutrition protocol resulted in significantly less time in the targeted 4.4-8.0 mmol/L BG band (85.6% Fixed vs. 89.0% Var., P = 0.018), and more hyperglycaemia (1.6% Fixed vs. 0.7% Var., P = 0.07), although these differences may not be clinically significant.

The current variable nutrition protocol and the CB stepped nutrition protocols had very similar GC safety, with similar numbers of patients who experienced mild hypoglycaemia (BG $<$ 4.0 mmol/L) (77 vs. 78, P = 1.00). Whereas, the fixed and SLQ stepped nutrition protocols resulted in slightly more cases of mild hypoglycaemia (82 vs. 77, P = 0.71 for both). However, the SLQ stepped nutrition protocol almost halved the number of severe hypoglycaemic (BG $<$ 2.22 mmol/L) cases (9 vs. 5, P = 0.42). In all cases, these results were measurable, but not statistically significant due to the low numbers considered.

Table 8.2: Comparison of the per-patient virtual trial GC performance results for the 4 simulated nutrition protocols.

| Nutrition protocol | Variable | Fixed | CB stepped | SLQ stepped | P-Values | | |
|---|---|---|---|---|---|---|---|
| | | | | | Var vs. Fixed | Var vs. CB stepped | Var vs. SLQ stepped |
| *GC Performance* | | | | | | | |
| BG median (mmol/L) | 6.2 [6.0 - 6.7] | 6.3 [6.0 - 6.9] | 6.3 [6.0 - 6.7] | 6.2 [6.0 - 6.7] | 0.24 | 0.89 | 0.61 |
| BG mean (mmol/L): | 6.4 [6.20 - 6.9] | 6.5 [6.2 - 7.2] | 6.4 [6.2 - 6.9] | 6.4 [6.2 - 6.9] | 0.17 | 0.75 | 0.57 |
| BG SD (mmol/L): | 1.2 [0.9 - 1.7] | 1.3 [0.9 - 1.9] | 1.2 [0.9 - 1.7] | 1.2 [0.9 - 1.7] | 0.05 | 0.89 | 0.84 |
| % BG <2.22 mmol/L | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] | 0.0 [0.0 - 0.0] | 0.81 | 0.65 | 0.28 |
| % BG <4.4 mmol/L | 0.0 [0.0 - 3.6] | 0.0 [0.0 – 4.0] | 0.0 [0.0 - 3.8] | 0.0 [0.0 – 4.0] | 0.80 | 0.90 | 0.82 |
| % BG 4.4-8.0 mmol/L | 89.0 [75.8 - 94.7] | 85.6 [68.8 - 94.4] | 88.3 [76.2 - 95.7] | 89.5 [75.0 - 96.1] | 0.018 | 0.88 | 0.64 |
| % BG >10.0 mmol/L | 0.7 [0.0 - 5.3] | 1.6 [0.0 - 7.1] | 0.6 [0.0 - 5.6] | 0.6 [0.0 - 5.4] | 0.07 | 0.93 | 0.98 |
| Mean hourly insulin (U/hr) | 3.4 [2.1 - 4.6] | 3.7 [2.3 - 5.1] | 3.0 [1.8 - 4.4] | 3.0 [1.7 - 4.1] | 0.019 | 0.06 | 0.022 |
| *Safety* | | | | | | | |
| # patients BG <4.0 mmol/L | 77 | 82 | 78 | 82 | 0.71 | 1.00 | 0.71 |
| # patients BG <2.22 mmol/L | 9 | 10 | 11 | 5 | 1.00 | 0.82 | 0.42 |

*Cahill et al. best (CB), STAR lower quartile (SLQ), Glycemic Control (GC), blood glucose (BG), standard deviation (SD). Data presented in Median [inter-quartile range (IQR)] where appropriate.

The hourly resampled BG CDF for the first 3 days of ICU stay and overall are plotted in Fig. 8.5. The variable and both stepped nutrition protocols had very similar performance over the first 2 days of ICU stay. However, at day 3, where the CB stepped nutrition protocol exceeds the average achieved clinically in Fig. 8.4, the CB protocol experiences slightly more hyperglycaemia, as might be expected. The fixed nutrition protocol consistently under performs the other simulated nutrition protocols on all days.

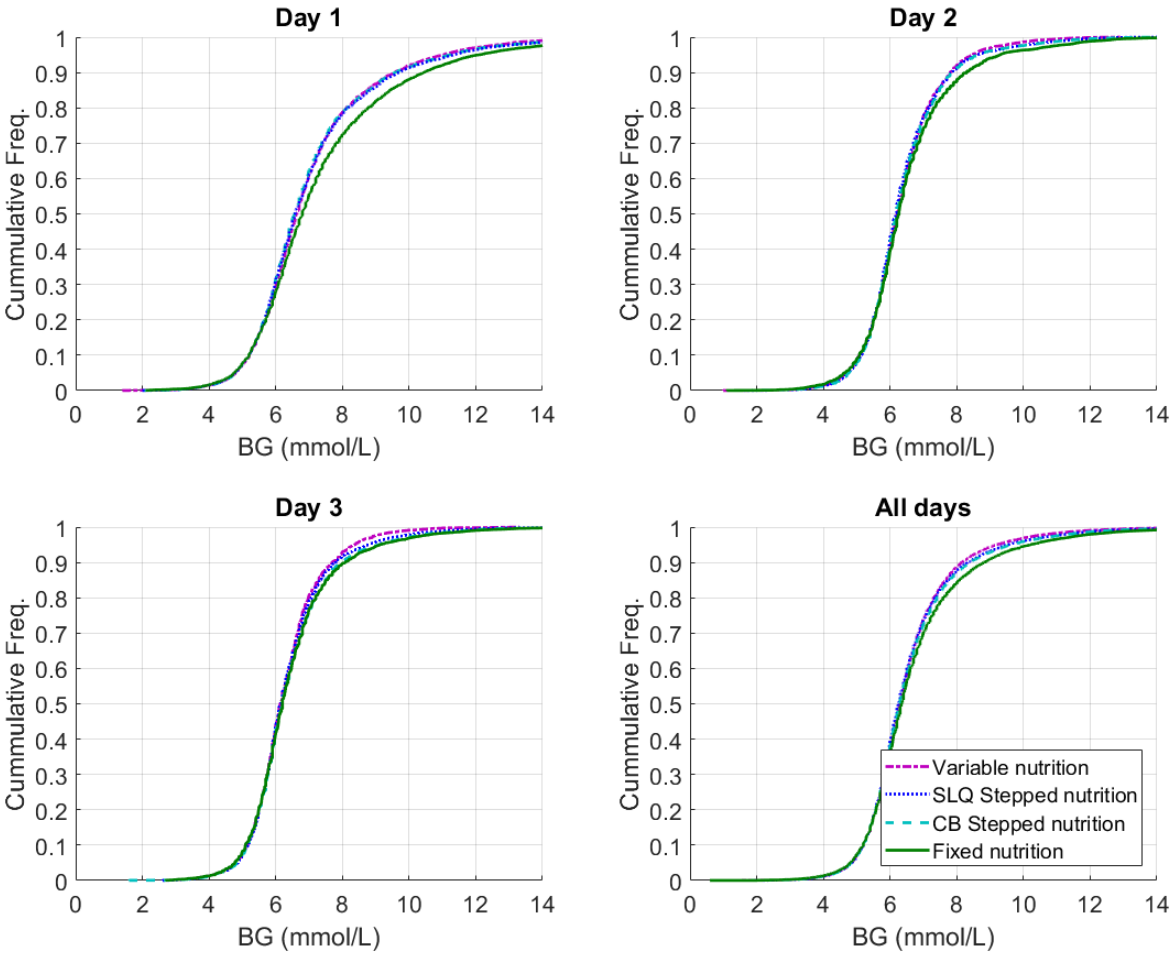



Figure 8.5: Resampled hourly BG cumulative distribution function (CDF) for each of the simulated nutrition protocols (Variable, Fixed, Cahill et al. best (CB) stepped, and STAR lower quartile (SLQ) stepped) on the first 3 days of Glycemic Control (GC) and for all time.

### 8.3.3 Workload

GC workload for each of the simulated nutrition protocols is given in Table 8.3. The fixed nutrition protocol and both stepped nutrition protocols had slightly higher numbers of BG measurements per day compared to the variable nutrition protocol (11.4 Var. vs. 13.4 Fixed, 12.0 CB and 12.0 SLQ, $P < 0.001$, $P = 0.004$, and $P = 0.011$ respectively), with an overall increase of total BG measurements required of 17.8% for fixed, 9.4% for CB stepped, and 7.0% for SLQ stepped. All four nutrition protocols had very similar numbers of insulin changes per day. However, as expected, the fixed and stepped nutrition protocols had significantly lower numbers of nutrition changes per day compared to the variable nutrition protocol (6.4 Var. vs. 0.0 Fixed and 0.5 for both CB and SLQ, $P < 0.001$ for all cases).

Overall, all 3 alternative nutrition protocols largely reduced the total number of clinical interventions (BG measurements, and insulin and nutrition rate changes) required (-14.6% Fixed, -18.3% CB and -19.8% SLQ), and thus GC workload. Note, the expected number of nutrition rate changes per day for the stepped nutrition protocols is 1. However, if a patient ends GC part way through a day, before a step in feed occurs, this statistic is slightly skewed.

Table 8.3: Comparison of the virtual trial GC workload results for the 4 simulated nutrition protocols.

| Nutrition protocol | Variable | Fixed | CB stepped | SLQ stepped | P-Values | | |
|---|---|---|---|---|---|---|---|
| | | | | | Var vs. Fixed | Var vs. CB stepped | Var vs. SLQ stepped |
| *Workload* | | | | | | | |
| Num. BG measurements | 10,237 | 12,060 (+17.8%) | 11,196 (+9.4%) | 10,956 (+7.0%) | - | - | - |
| Num. insulin changes | 6,759 | 6,964 | 6,626 | 6,542 | - | - | - |
| Num. nutrition changes | 5,270 | 0 | 370 | 370 | - | - | - |
| Total interventions | 22,266 | 19,024 (-14.6%) | 18,192 (-18.3%) | 17,868 (-19.8%) | - | - | - |
| *Per-patient treatment statistics* | | | | | | | |
| Num. BG measures/day: | 11.4 [10.1 - 13.7] | 13.4 [11.6 - 16.8] | 12.0 [10.6 - 14.7] | 12.0 [10.5 - 14.5] | <0.001 | 0.004 | 0.011 |
| Num. insulin changes/day | 7.5 [6.4 - 8.3] | 7.8 [6.5 - 8.9] | 7.4 [6.0 - 8.4] | 7.2 [6.1 - 8.4] | 0.026 | 0.31 | 0.21 |
| Num. nutrition changes/day: | 6.4 [4.4 - 8.0] | 0.0 [0.0 - 0.0] | 0.5 [0.2 - 0.7] | 0.5 [0.2 - 0.7] | <0.001 | <0.001 | <0.001 |
| Total Num. interventions/day: | 25.5 [21.7 - 30.0] | 21.5 [18.9 - 24.8] | 19.9 [17.7 - 23.1] | 19.8 [17.5 - 23.1] | <0.001 | <0.001 | <0.001 |

*Cahill et al. best (CB), STAR lower quartile (SLQ), blood glucose (BG). Data presented in Median [inter-quartile range (IQR)] where appropriate.

CDFs of the number of BG measurements per day, per patient, for the first 3 days of ICU stay and all time are plotted in Fig. 8.6. CDFs of BG measurements were plotted as opposed to overall workload, as they have the largest impact on clinical workload [272]. Initially, the variable nutrition and both stepped nutrition protocols had very similar BG measurement workload. However, as the days on GC progress, the fixed nutrition rate given to all patients increases, and, as a result, BG measurement workload for both stepped nutrition protocols increases. The fixed nutrition protocol consistently has higher BG measurement workload than all the other simulated nutrition protocols, and with respect to Fig. 8.3, is also *overfeeding* the greatest number of patients.

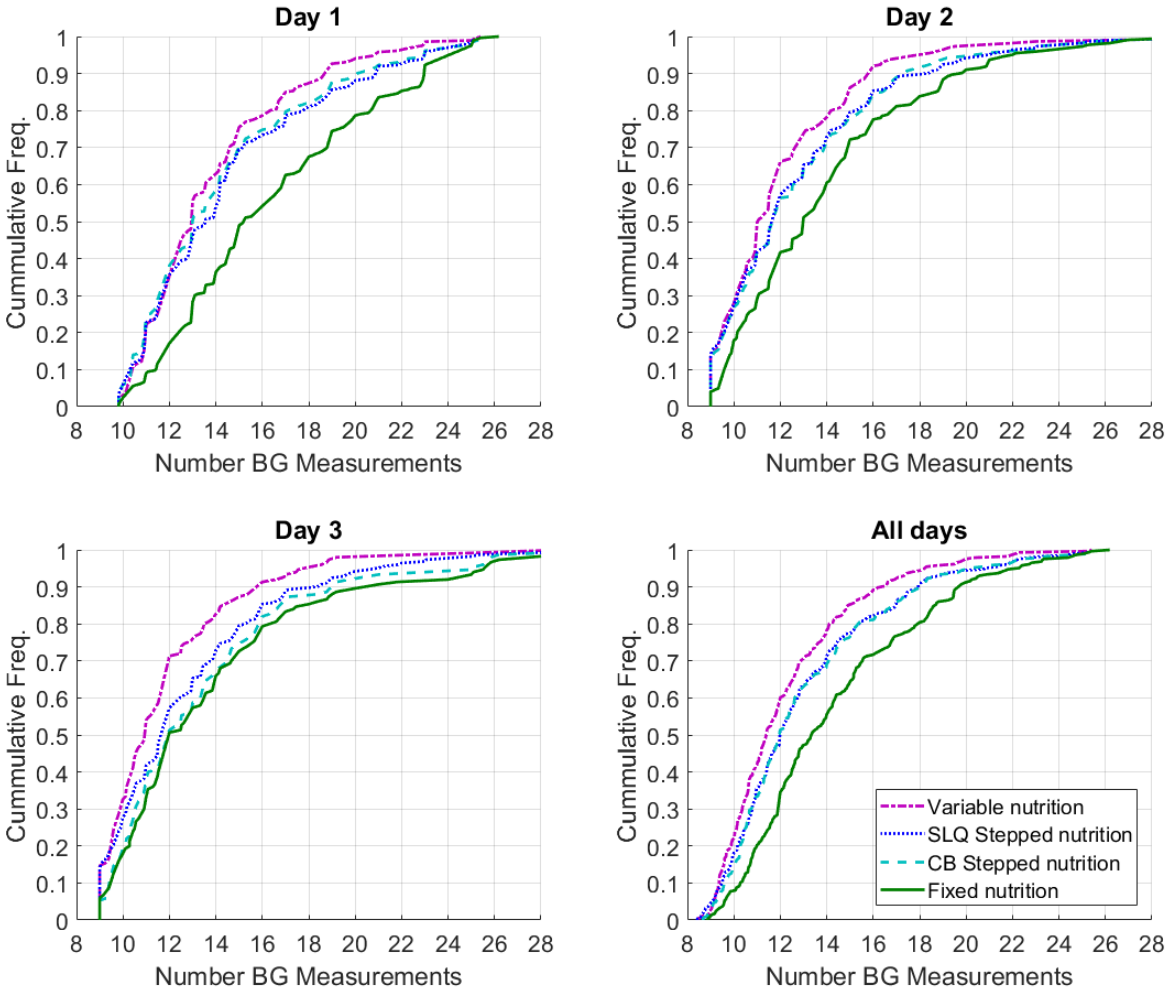



Figure 8.6: The cumulative distribution function (CDF) of the mean number of blood glucose (BG) measurements per day, per patient, for each of the simulated nutrition protocols (Variable, Fixed, Cahill et al. best (CB) stepped and STAR lower quartile (SLQ) stepped) on the first 3 days of Glycemic Control (GC) and for all time.

## 8.4 Discussion

From Fig. 8.4, the difference in the nutrition protocols simulated on the virtual STAR cohort is evident. All the alternative nutrition protocols proposed deliver considerably more nutrition, over the first 3 days of ICU stay, and thus the majority of patients, than the best ICU surveyed by Cahill et al. [263].

### 8.4.1 Variable vs Fixed nutrition

The fixed nutrition protocol (100% caloric goal) had slightly worse GC performance compared to the variable nutrition protocol in Table 8.2 (P = 0.018) and Fig. 8.5, with considerably more hyperglycaemia (P = 0.07, Table 8.2). This result can be largely attributed to the higher nutrition rate *overfeeding* a greater number of patients, based on Fig. 8.3. These issues result in increased BG and increased insulin dose (3.7 vs. 3.4 U/hr, P = 0.019), which in some cases saturates the maximum *'safe'* insulin dose allowed ($\leq$ 9 Units/hour) by STAR. At this point, only lowering nutrition given would enable reductions to intermediate BG levels in the 4.4-8.0 mmol/L range, due to the saturation of insulin action [225], [287]. In addition, as the fixed nutrition protocol required more insulin, it thus created a greater risk of hypoglycaemia in response to patient variability. Thus, 5 (6.5%) more patients experienced mild hypoglycaemia than the variable nutrition protocol (P = 0.71, Table 8.2), illustrating the reduced safety with the high fixed nutrition protocol.

The fixed nutrition protocol also resulted in 2 more BG measurements required per day (P<0.001, Table 8.3), with a 17.8% increase overall in total number of BG measurements required. This result can again be attributed to *overfeeding* most or all patients, resulting in more BG measurements above the targeted 4.4-8.0 mmol/L BG band and thus more hourly measurements being required by STAR [128], [147]. The changes in insulin interventions were very similar between protocols (P = 0.026, > 0.016, Table 8.3), and, as expected, the number of nutrition changes were significantly lower (P < 0.001, Table 8.3). Therefore, overall, compared to variable nutrition protocol the total number of interventions required is reduced by 14.6%, largely reducing clinical staff workload, but with a consequent decrease in GC performance and safety.

### 8.4.2 Variable vs CB Stepped nutrition

The CB stepped nutrition protocol provided very similar GC performance to the variable nutrition protocol in Table 8.2 (P = 0.88) and Fig. 8.5. The largest loss in GC performance in Fig. 8.5 occurs during day 3, which is most likely due to the CB stepped nutrition protocol feeding 100% caloric goal on this day, to all patients, compared to the variable nutrition protocol, feeding on average 87% caloric goal (Fig. 8.4), with a wide variability across patients (Fig. 8.3). Thus, there are increasing numbers of *overfed* patients as days on GC progress with the CB protocol.

Safety was also very similar in Table 8.2, but there were 2 more cases (0.7%) of severe hypoglycaemia (P=0.82). Both episodes occurred when the CB protocol was delivering 100% caloric goal. This outcome clearly emphasises the strong trade-off between achieving high nutrition targets and achieving safe, and effective GC.

The CB stepped nutrition protocol resulted in 0.6 more BG measurements required per day (P = 0.004, Table 8.3), with a 9.4% increase overall in total number of BG measurements required. The slight increase in BG measurements is consistent in each of the CDFs presented in Fig. 8.6. This increase in BG measurements may be due to the intra-day inflexibility of the CB stepped nutrition protocol resulting in less effective treatment options being offered to some patients, given the clinical patient-specific nutrition variability seen in Fig. 8.3.

In general, the difference in workload occurs where an insulin increase and nutrition lowering was offered previously by variable nutrition protocol, but now only an insulin increase was able to be offered by the CB stepped nutrition protocol, limiting STAR's ability to effectively lower BG. This limitation results in patients spending a slightly greater duration outside the targeted 4.4-8.0 mmol/L BG band, thus requiring more 1-hourly measurements per the STAR protocol.

In contrast, the number of insulin changes per day was very similar between the two nutrition protocols (P = 0.31, Table 8.3). However, again, there was a significant reduction in the number of nutrition changes required per day (P<0.001, Table 8.3). Therefore, overall, compared to variable nutrition protocol, the total number of interventions required is reduced by 18.3%, further reducing

clinical staff workload, while maintaining a similar GC performance. However, due to *overfeeding* still occurring for many patients, based on Fig. 8.3, especially after day 3 at 100% goal feed rate, a slight decrease in safety occurs.

### 8.4.3 Variable vs SLQ Stepped nutrition

The SLQ stepped nutrition protocol provided very similar GC performance to the variable nutrition protocol in Table 8.2 (P=0.64) and Fig. 8.5. From Fig. 8.5 a small loss in GC performance occurs during day 3, which is, again, most likely due to the intra-day inflexibility of the stepped nutrition protocols, as mentioned above. The SLQ stepped nutrition protocol resulted in 5 more patients who experienced mild hypoglycaemia (P = 0.71, Table 8.2). However, it largely reduced insulin requirements (3.0 vs. 3.4 U/hr, P = 0.022 Table 8.2), and as a result, almost halved the number of severe hypoglycaemia cases (5 vs. 9, P = 0.42 Table 8.2), greatly improving patient safety. In essence, severe hypoglycaemic events were improved to mild events. This outcome further illustrates the fine balance between achieving nutrition targets, not under or over feeding individual patients, and achieving safe, and effective GC.

The SLQ stepped nutrition protocol resulted in 0.6 more BG measurements required per day (P = 0.011, Table 8.3), with a 7.0% increase overall in total number of BG measurements required. This slight increase is again consistent in each of the CDFs presented in Fig. 8.6, although the SLQ stepped protocol at least slightly *under feeds* approximately 75% of patients each day by definition compared to the maximum possible uptake. Thus, the increased BG measurements again may be due to the intra-day inflexibility of the SLQ stepped nutrition protocol.

In contrast, the number of insulin changes per day was very similar between the two nutrition protocols (P = 0.21, Table 8.3). However, again, there was a significant reduction in the number of nutrition changes required per day (P<0.001, Table 8.3). Therefore, overall, compared to variable nutrition protocol the total number of interventions required is reduced by 19.8%, the largest reduction in clinical staff workload, while maintaining similar GC performance and offering improved safety.

### 8.4.4 Limitations

The mean nutrition rate achieved by the best unit surveyed by Cahill et al. [263] was still considerably lower than the predetermined ACCP caloric goal over the first 3 days, suggesting these generalised approximations do not represent all patients well, as seen in Fig. 8.3 and Chapter 7. This reduction is likely due to patients being unable to tolerate the 100% feeding, resulting in high gastric residuals and other negative effects. In addition, the patient-specific *'ideal'* nutrition rates presented in Fig. 8.3 are dependent on the carbohydrate content of the feed type given. Hence, considering that the *'ideal'* nutrition rate is in relation to a patient's glucose tolerance, and the glucose content of feed types used vary across ICUs, the percentage caloric goal a cohort can tolerate is likely ICU specific. However, this value could be easily changed to be in terms of only glucose concentration to allow better integration into other ICUs, with varying feed types.

Virtual trials have been shown to give a good indication of expected clinical performance [230], [295] and be generalizable across ICUs [154]. However, they do not allow for unforeseen clinical exceptions, such as the gastric residuals or malnutrition of a patient, and the likely associated increased workload with these effects. In addition, this analysis did not consider the clinical feed stoppages that occurred clinically for each patient. However, considering this analysis was not comparing to other clinical protocols and only between virtual trials, it was deemed not necessary. Therefore, the results only represent an *'ideal'* situation and remain to be confirmed, and a prospective clinical trial should be undertaken. However, the rates of nutrition given here do suggest malnutrition is not occurring, as all rates were in the optimal middle tertile of the work in [100]. Overall, the virtual in silico design analysis presented has improved the likelihood of a successful clinical implementation. The STAR GC protocol, uses model-based, patient-specific control in conjunction with a stochastic model to predict the best treatment for a patient. As shown by the GC results, irrespective of the nutrition protocol, STAR is able to achieve very good GC. However, in many clinical practices protocolised changes in the nutrition rate given to a patient for GC is foreign, and thus clinically unacceptable. Thus, the main focus of this study is to suggest alternative nutrition protocol options that may be more clinically acceptable, and show the associated consequences for each. However, as this study

is only strictly a virtual trial, a clinical trial of these different nutrition protocols would be required to further confirm these results in the face of real-life, clinical compliance.

## 8.5 Summary

STAR is a model-based GC protocol that uniquely maintains normo-glycaemia by changing both insulin and nutrition interventions, and has been proven effective in controlling BG in the ICU. However, most ICU GC protocols only change insulin interventions, making the variable nutrition aspect of STAR less clinically desirable. Therefore, three alternative, simpler and lower workload nutrition protocols were investigated using clinically evaluated virtual trials.

All the alternative nutrition protocols reduced the total intervention workload considerably (14.6 - 19.8%). However, only the stepped (by day) nutrition protocols achieved similar GC performance to the current variable nutrition protocol. Of the two stepped nutrition protocols, the SLQ stepped nutrition protocol also improved GC safety, almost halving the number of severe hypoglycaemic cases (5 vs. 9, $P = 0.42$), while still providing nutrition delivery near equal to the best ICU in an international context. Overall, the SLQ stepped nutrition protocol was the best alternative to the current variable nutrition protocol, but either of the stepped nutrition protocols could be adapted by STAR to reduce workload and make it more clinically acceptable. Overall, these virtual trials indicate a strong 3 sided trade-off between high nutrition rate, safe, effective GC and total workload.

While virtual trials have shown to be very good in part, a clinical trial should be undertaken to confirm the results of this study. The overall results of this study should further the clinical flexibility of STAR for differing clinical practices. However, the existing STAR implementation needs to be developed to better allow changes to be made within the framework.

# Chapter 9

# Design of a STOMP controller

## 9.1 Background

The STAR GC protocol recommends interventions based on a clinically specified maximum risk of light hypoglycaemia (BG $<$ 4.4 mmol/L), derived from stochastic model predictions of future $S_I$, as detailed in Section 1.2.4 and Chapter 3 [145], [149]. With the ability to quantify the probability of hypoglycaemia, STAR allows aggressive yet safe control of BG within a target band. STAR is flexible to different BG targets [229], [296] and clinical staff intervention frequency, and thus addresses many of the areas required for clinical implementation.

However, the heuristic intervention selection algorithm used by STAR is fixed and does not allow for dynamic tuning [128], limiting the capacity for the controller to be further optimized in real time. In particular, it uses multi-layered condition statements to select the desired intervention from a pool of allowed interventions. Overall, the multiple conditions and layers are conceptually complex, making tuning of the controller response difficult.

[1] **K. W. Stewart**, C. G. Pretty, H. Tomlinson, L. Fisk, G. M. Shaw, and J. G. Chase, "Stochastic Model Predictive (STOMP) glycaemic control for the intensive care unit: Development and virtual trial validation," Biomed. Signal Process. Control, vol. 16, pp. 61–67, Feb. 2015.

[2] **K. W. Stewart**, C. G. Pretty, H. Tomlinson, L. Fisk, G. M. Shaw, and J. G. Chase, "Stochastic Model Predictive Glycemic Control for the Intensive Care Unit: Development and virtual trial validation," in 14th Annual Diabetes Technology Meeting, 2014, pp. 342–485.

MPC is an alternative control approach that allows the dynamic response of the controller to be easily tuned through a series of clinically pre-defined cost functions. MPC utilizes a mathematical model of a system to forecast the response to a given input, and control interventions are chosen to produce optimal forecasted results. Commonly, optimization will involve specifying cost functions to key input and output performance metrics, and choosing an intervention that minimizes the overall summed total cost. Thus, cost functions provide a mathematical alternative to what is currently done with multiple condition statements.

The benefit of such a system is that the cost functions can be easily optimized to produce robust and consistent control outcomes from an intuitively and easily understood clinical specification. This type of controller is thus investigated due to the flexibility of cost functions, allowing the dynamic response of the controller to be easily tuned, improving on the clinical flexibility that can be offered by STAR. More specifically, the relative weighting of insulin minimization for safety, and nutrition maximisation for recovery, can be modified more easily via cost functions. MPC is also a proven effective technique for GC, with many implementations of different models already [214], [232], [297]–[301].

This chapter presents a Stochastic Model Predictive (STOMP) GC protocol that uses an infrequently measured BG signal to control the BG levels of adult ICU patients, while providing greater flexibility than the STAR GC protocol. This chapter presents the STOMP protocol design and optimization for an adult ICU using clinically evaluated virtual trials [154], [230] to amend safety and efficacy before clinical utilization.

## 9.2 Methods

### 9.2.1 Control methodology overview

STOMP is designed to combine the methodology of MPC with the stochastic prediction used within the STAR framework. Similar to STAR, STOMP initially requires 2 BG measurements [128]. After 2 BG measurements are taken, integral based parameter fitting [153] is used to identify the current model-based $S_I$, per Section 4.2.1 *Identification of insulin sensitivity ($S_I$)* [31], [148], [154]. This value is then used with the stochastic model in Chapter 3 *Evaluation and simplification of STAR's stochastic model* [128], [145], [149], to find the $5^{th}$ and $95^{th}$ percentile potential future $S_I$ values. These $5^{th}$ and $95^{th}$ percentile $S_I$ values, and a potential insulin and nutrition intervention, are then used to forward-simulate the likely resulting $5^{th}$ and $95^{th}$ percentile BG values, for that potential intervention. The potential intervention and associated forward simulated BG outcome are then evaluated in a series of cost functions, and a cost assigned to that intervention. This process is repeated over all the possible interventions to find the intervention with the lowest evaluated cost, the optimal intervention. These steps are summarised in Fig. 9.1.

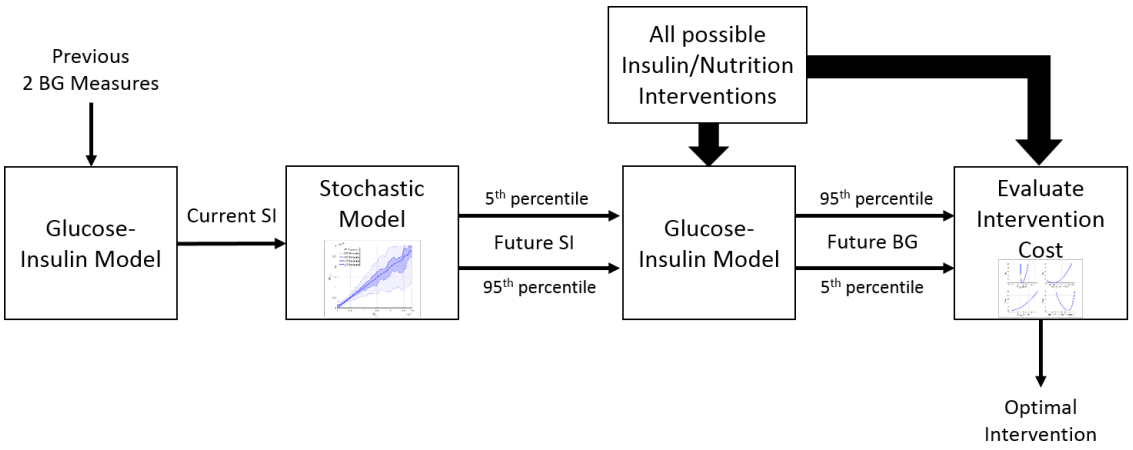



Figure 9.1: The Stochastic Model Predictive (STOMP) Glycemic Control (GC) protocol flow diagram.

#### *9.2.1.1 Clinical implementation*

ACCP guidelines are used to estimate the patient's daily caloric goal [156]. STOMP modulates nutrition rate between 30-120% of caloric goal in steps of 5%, with a maximum change of ±30% caloric goal per hour. Insulin is administered by infusion, rather than bolus, and is modulated between 0-9 U/hr (0-150 mU/hr) in steps of 0.5 U/hr, with a maximum increase of 2 U/hr.

Similar to the current version of STAR, if a patient's BG is currently within the targeted BG band (4.4-8.0 mmol/L), clinical staff have the flexibility to choose between 1-3 hour measurement intervals. However, if a patient's BG is outside the targeted BG band, clinical staff are limited to hourly measurements. In this studies simulation the maximum measurement interval offered by either STAR or STOMP was always selected. In addition, a 4 hour measurement interval, while patients were in the targeted band, was also investigated with the STOMP protocol.

### 9.2.2 Model prediction

#### *9.2.2.1 Glucose-Insulin model*

A modified version of the ICING model, Section 1.2.4.1 *ICING Model*, was used to describe and predict the glucose-insulin metabolic system dynamics in the STOMP GC protocol. This model requires the future model-based $S_I$ and given interventions to forward-simulate the future BG trajectory. The future model-based $S_I$ is provided by the stochastic model of Fig. 9.2, and given interventions are iteratively selected from the pool of all possible interventions.

#### *9.2.2.2 Stochastic prediction*

A conditional probability density function (PDF) of $S_I$, based on historical patient data [145], [149], is used to predict expected future $S_I$ range (the stochastic model). Given a value of $S_I$ at hour n, the probability of future $S_I$ values at hour n+1 can be estimated, see Fig. 9.2. The stochastic model used by STOMP is the same stochastic model currently used by STAR, generated using kernel-density methodology in combination with the model-based $S_I$ data from a large cohort of patients (>23,000 hours) [145], as described in Chapter 3. The stochastic model covers a broad medical ICU cohort over all the days of stay, and, if required, can be made specific to unique cohorts [122], [262].

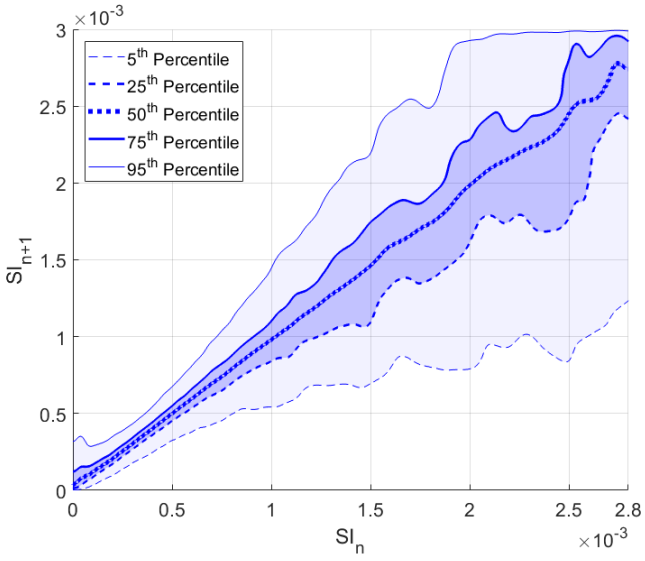



Figure 9.2: The stochastic model of insulin sensitivity ($S_I$) used by the Stochastic Model Predictive (STOMP) Glycemic Control (GC) protocol.

The future $S_I$ PDF obtained from Fig. 9.2 can then be used to find the future BG PDF, for a specific insulin and nutrition intervention, by forward solving the Glucose-Insulin model, as illustrated in Fig. 9.3 [145]. Like STAR, STOMP focusses on the $5^{th}$ and $95^{th}$ percentile values of the stochastic model, as these values can be used to impose a 5% risk limit on hypoglycaemia for a given insulin and nutrition intervention. Note, the $5^{th}$ percentile $S_I$ corresponds to the $95^{th}$ percentile BG value and the $95^{th}$ percentile $S_I$ corresponds to the $5^{th}$ percentile BG value.

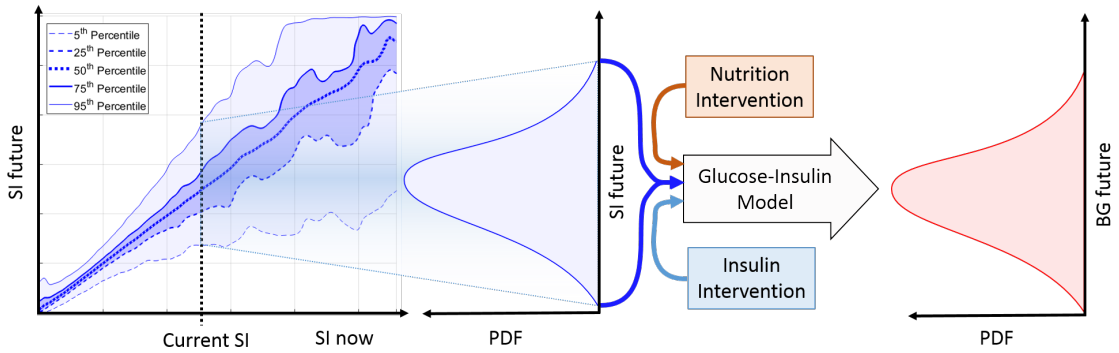



Figure 9.3: Using the stochastic model of insulin sensitivity ($S_I$) to find the probability density function (PDF) of blood glucose (BG), for a given insulin and nutrition intervention.

#### *9.2.2.3 Prediction horizon*

Prediction horizons of 1 to 10 hours were initially investigated. The nutrition and insulin interventions chosen are kept constant over the prediction horizon to encourage minimal intervention changes, and

thus encourage reduced clinical workload. In addition, the $5^{th}$ and $95^{th}$ percentile $S_I$ values are kept constant over the prediction horizon as the previously identified $S_I$ value is most likely to stay approximately at its current value, as seen by the mode in Fig. 9.2 being at no change in value. Note, the model was evaluated up to the prediction horizon for treatment assessment, but BG measurements occurred every 1-4 hours, during which the model prediction was re-evaluated.

Initial simulations highlighted two factors that limited the prediction horizon. Insulin and nutrition changes have differing time scales, with insulin changes having a rapidly observable effect (<10 minutes), while EN changes act over 1-2 hours due to the slower, more complex absorption dynamics through the stomach and gut [220], [302]. Thus, the predicted BG outcomes over longer prediction horizons include a greater contribution from intervention changes in EN.

In addition,$S_I$ fluctuates each hour. Thus, the current fitted $S_I$ value becomes more inaccurate as the prediction horizon increases. Equally, constant insulin and nutrition over the prediction interval means the model eventually reaches a steady-state. Typically, steady-state was reached after approximately 6 hours, thus limiting the maximum horizon to this maximum value.

### 9.2.3 Cost functions

The cost functions used to evaluate the multiple different interventions can be seen in Fig. 9.4. These cost functions were chosen iteratively using virtual trials to optimize the likely GC results. They are also strongly based on clinical and physiological literature, and clinical experience with prior protocols. The functions are designed to manage risk trade-offs between BG outcomes, and the insulin and nutrition interventions given.

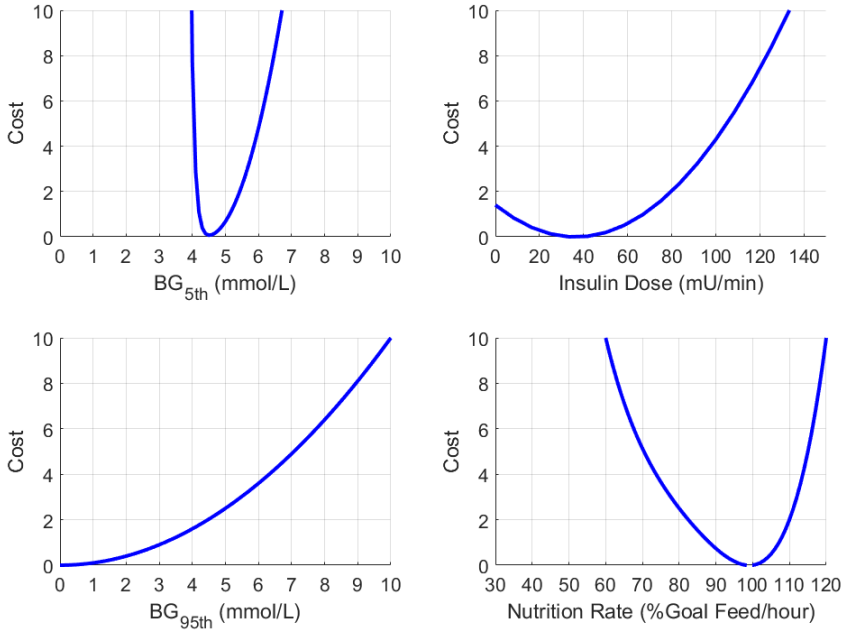



Figure 9.4: Cost functions used with the Stochastic Model Predictive (STOMP) Glycemic Control (GC) protocol to evaluate the optimal insulin and nutrition intervention.

The $5^{th}$ and $95^{th}$ percentile BG cost functions were designed to severely penalize both hyper- and hypo- glycaemia, and thus keep the predicted $5^{th}$ and $95^{th}$ percentile BG range within the desirable targeted band [34]. The $5^{th}$ percentile BG cost function was generated by combining an exponential and $2^{nd}$ order polynomial function, severely penalizing BG $< 4.0$ mmol/L, ensuring hypoglycaemia was very unlikely to occur, while not forcing the controller to be too aggressive in lowering BG. The $95^{th}$ percentile BG cost function is a $2^{nd}$ order polynomial with a strong emphasis on reducing the incidence of hyperglycaemia. The equations for these two cost functions are defined:

$$Cost_{BG\ 5th} = 1.875 \times {BG_{5th}}^2 - 16.5 \times BG_{5th} + 36.3 + \exp^{-10 \times BG_{5th} + 42} \tag{9.1}$$

$$Cost_{BG\ 95th} = 0.1 \times {BG_{95th}}^2 \tag{9.2}$$

Where: $BG_{5th} = 5^{th}$ *Percentile predicted blood glucose value* $(mmol/L)$,

$BG_{95th} = 95^{th}$ *Percentile predicted blood glucose value* $(mmol/L)$

The insulin and nutrition cost functions were designed to maximize nutrition and minimize insulin use. This choice ensures the patient is getting as much of the desired caloric goal nutrition rate as possible, while minimizing the chance of BG falling dramatically due to the large insulin doses, amplifying the effects of $S_I$ variability [122], [254], [288], [292]. Hence, it is a balance of maintaining maximum nutrition intake and patient safety, as discussed previously in Chapter 8 *Simpler STAR nutrition protocols*. The equations for these two cost functions are defined:

$$Cost_{Insulin} = 0.001 \times {U_{ex}}^2 - 0.078 \times U_{ex} + 1.255 \tag{9.3}$$

$$Cost_{Nutrition} = 7.292 \times 10^{-6} \times GF^4 - 2.469 \times 10^{-3} \times GF^3 + 0.3158 \times GF^2 - 18.26 \times GF + 407.8; \tag{9.4}$$

Where: $U_{ex} = Insulin\ dose\ prescribed\ (mU/hr)$,

$GF = Percentage\ of\ goal\ feed/hour\ prescribed\ (\%/hr)$

Pancreatic insulin secretion in the critically ill can be highly variable and unpredictable. Thus, maintaining a low insulin dose can dominate pancreatic insulin secretion [122] and provide greater certainty around circulating plasma insulin for model-based predictions. Hence, the minimum of the insulin cost function is placed at 2 U/hr (33 mU/min) to increase this predictability.

The mathematical equations for the insulin and nutrition cost functions were derived by fitting a $2^{nd}$ and $4^{th}$ order polynomials to the shape desired by clinical staff consultation. The cost function polynomials were designed to have a clear global minima in the range at which the functions would be applied. The use of polynomials means the cost functions are smooth, and thus continuously differentiable in optimization with a unique global minimum, due to their convex definition.

### 9.2.4 Blood glucose cost function weightings

In addition to the 1, 2, 3, 4, 5, and 6 hour forward predicted BG $5^{th}$ and $95^{th}$ each being evaluated in the BG cost functions, weightings were also placed on each of the hourly BG prediction costs, increasing the relative importance of BG outcome timing. Each of the evaluated costs were increasingly weighted as the BG prediction time increased, see Eq. (9.5). Therefore, more importance was placed on the far future BG outcome, near the end of the prediction horizon, rather than the immediate BG response to encourage treatments which don't require future modification. A normalized weighting sum was maintained of the total cost value, see Eq. (9.5).

$$W_i = (\frac{2}{N} - \frac{1}{\sum_{j=1}^{N} j})\frac{i}{N} \tag{9.5}$$

$$\text{i.e.} \quad W_2 = 2 \times W_1, \; W_3 = 3 \times W_1 \; etc.$$

$$\sum_{i=1}^{N} W_i = 1 \tag{9.6}$$

Where: $W_i$ = Normalized increasing weight, $i$ = BG prediction hour (1-N hours),

$N$ = Prediction window period

In addition to the time dependent weighting on hourly BG predictions, an additional weighting was placed on the overall summed BG prediction costs. This weighting ranks the evaluated BG prediction costs higher than the insulin and nutrition cost. Iteratively, it was found that a weighting of 6 on the BG prediction costs gave the best glycaemic performance, while still maintaining reasonable nutrition and insulin levels within virtual trial simulations. The final cost calculation can be seen below:

$$\text{Intervention Cost} = 6 \times (\sum_{i=1}^{N} W_i \times (Cost_{BG\ 5th,i} + Cost_{BG\ 95th,i})) + Cost_{Insulin} + Cost_{Nutrition} \tag{9.7}$$

### 9.2.5 Patient cohort and virtual trials

Clinical data from 149 patients treated with the STAR protocol (2011-2014) [128], [229], in Christchurch Hospital ICU, NZ were used to generate virtual patients. Details of these patients are shown in Table 9.1. The Upper South Regional Ethics Committee, New Zealand granted approval for the audit, analysis and publication of this data. Note, this controller was developed before assessment of the larger STAR cohort in Chapter 5 *Clinical performance review of the STAR Glycaemic Control protocol*, and thus was not used for virtual trials.

Table 9.1: Demographic details of the STAR cohort used for virtual trials.

| | |
|---|---|
| Number of Patients | 149 |
| Age | 64 [54 - 72] |
| Gender (% Male) | 66.7 |
| Length of ICU Stay (Days) | 8.4 [3.5 - 16.0] |
| # Operative/Non-operative | 49/100 |
| APACHE II score | 21.0 [15.0 – 25.0] |
| Length of GC (hours) | 73.4 [43.2 - 135.7] |
| Cohort total GC (hours) | 17,610 |

*Acute Physiology And Chronic Health Evaluation (APACHE), Glycemic Control (GC). Data presented as median [inter-quartile range (IQR)] where appropriate.

Virtual patients were created from the patient-specific time varying model-based $S_I$ profiles [153]. This model-based $S_I$ can be used as a critical marker of a patient's metabolic state [112], [145], [230]. These virtual patients allow robust protocols to be safely designed and rigorously tested prior to clinical implementation, improving patient safety and minimising the need for protocol alterations post- implementation [154], [230].

### 9.2.6 Analysis and statistics

STOMP was compared to STAR in terms of GC safety, performance, and workload. The metrics assessed comprise of:

**Safety:**
- Number of severe hypoglycaemia patients (Number of patients with BG $< 2.2$ mmol/L) [35] [34].

**Performance:**
- Percentage of time in targeted BG band (4.4-8.0 mmol/L) [61], [142].
- Percentage of time hyperglycaemia occurs (BG $> 10$ mmol/L).

**Workload:**
- Mean number of BG measurements per day.

Due to the irregular 1-3 hourly measurement intervals, used in both STAR and STOMP, patient BG data was analysed with linear interpolation at 60 min intervals to enable fair comparisons [246], per Chapter 2 *Interpretation of Retrospective BG Measurements*. Note, minutely sampling was not used as this analysis was done before the analysis of Chapter 2 had been performed. As a consequence the BG percentage of time out of the targeted band statistics may be slightly conservative, although very unlikely to be significant, see Chapter 2.

STAR clinical data is presented for comparison with the virtual trial results of STAR. As the current implementation of STOMP only provides insulin via infusion, an infusion-based virtual trial of STAR is also presented for direct comparison. As noted, both STAR and STOMP allow variable measurement intervals, based on the BG history, and the maximum allowed measurement interval was always selected in these virtual trials. Both 3 and 4 hour maximum measurement intervals are shown for the STOMP protocol. Clinically, STAR uses a 3-hour maximum measurement interval.

## 9.3 Results

GC safety, performance, and workload for STAR clinical, and simulated STAR and STOMP protocols are shown in Table 9.2. Both STOMP and STAR provided very good GC performance, with very similar percentages of time in the targeted 4.4-8.0 mmol/L BG band (approximately 87.0% for both protocols), in all cases. Equally, the safety of both protocols was very high with less than 3.4% of patients experiencing a severe hypoglycaemic episode (BG $<$ 2.2 mmol/L). However, because STOMP optimises treatment and performance over a 6 hour prediction window, the selected treatment options have better foresight. As a result, STOMP was able to maintain excellent GC performance and safety with both 3 and 4 hour measurement intervals, while largely reducing the average number of measurements required per day (approximately 13 vs. 10.0 and 8.4 measures per day, respectively), which represent significant workload reductions [101], [151], [272].

A randomly selected virtual patient was chosen to show how STAR and STOMP respond to fluctuating $S_I$ in Fig. 9.5. The total cost associated with each chosen STOMP intervention can be seen to be constantly minimized, targeting the optimum balance of BG outcome and intervention cost for the patient, based on the pre-selected weights and cost functions. While, overall, the BG is largely similar between protocols, the insulin and nutrition interventions vary significantly, illustrating the differences between approaches.

Table 9.2: Clinical and virtual trial cohort performance of the STAR and STOMP Glycaemic controllers on STAR Cohort. STAR Clinical (Bolus) shows actual clinical performance of STAR. The other columns indicate virtual trial performance on this same cohort using bolus or infused insulin, with maximum measurement intervals as indicated.

| | STAR | | | STOMP | |
|---|---|---|---|---|---|
| | Clinical (Bolus) | 3hr max meas. Bolus | 3hr max meas. Infusion | 3hr max meas. Infusion | 4hr max meas. Infusion |
| *Workload* | | | | | |
| Mean num. measures/day | 13.4 | 13.2 | 12.7 | 10.0 | 8.4 |
| *Safety* | | | | | |
| % time BG <4.4 mmol/L | 1.7 | 2.7 | 3.2 | 1.9 | 2.8 |
| % time BG <2.2 mmol/L | 0.006 | 0.01 | 0.05 | 0.04 | 0.06 |
| Number of patients BG (%) <2.2 | 3 (2.0%) | 2 (1.3%) | 4 (2.7%) | 4 (2.7%) | 5 (3.4%) |
| *Performance* | | | | | |
| % time BG 4.4 - 7 mmol/L | 61.0 | 75.4 | 73.2 | 76.8 | 73.5 |
| % time BG 4.4 - 8.0 mmol/L | 80.6 | 87.5 | 86.3 | 87.7 | 86.2 |
| % time BG 8.0 - 10 mmol/L | 12.6 | 7.9 | 8.6 | 7.7 | 8.2 |
| % time BG >10 mmol/L | 5.1 | 2.5 | 2.6 | 3.2 | 3.2 |
| Goal feed median [IQR] (%) | 75.9 [36.4 - 99.4] | 90.2 [30.7-100.0] | 84.8 [30.5- 100.0] | 80.0 [65.0 - 95.0] | 80.0 [65.0 - 95.0] |
| Insulin rate median [IQR] (U/hr) | 2.5 [1.0 - 4.0] | 3.0 [1.5 - 5.5] | 4.0 [1.5 - 6.0] | 4.0 [2.0 - 5.5] | 4.0 [2.0 - 5.5] |

*Stochastic TARgeted (STAR), Stochastic Model Predictive (STOMP), blood glucose (BG), inter-quartile range (IQR).

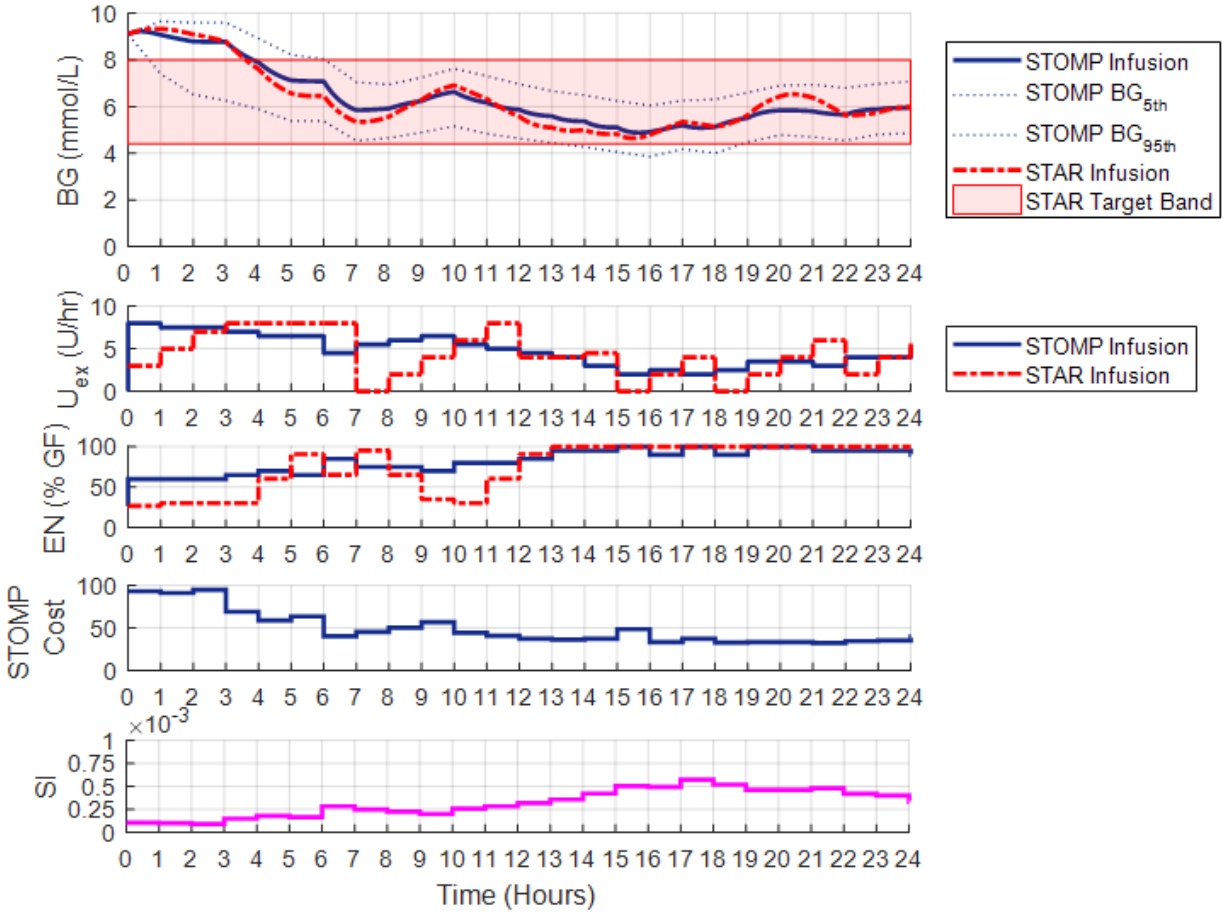



Figure 9.5: An example virtual patient showing the performance of Stochastic Model Predictive (STOMP) and Stochastic TARgeted (STAR) GC protocols. The STAR targeted blood glucose (BG) band (4.4-8.0 mmol/L) is also shown for comparison of performance.

## 9.4 Discussion

Table 9.2 shows STOMP performed very well providing safe and effective GC approximately equal to that of both STAR controllers, infusion and bolus. Both STAR and STOMP protocols provided a high percentage of time in the targeted BG (approximately 87%), while also ensuring patient safety ($< 0.06\%$ time of BG $< 2.2$ mmol/L). Equally, the number of patients who experienced severe hypoglycaemia (4-5 or 2.7-3.4% of patients BG $< 2.2$ mmol/L) were very low compared to other reported GC protocols [105], [109], [213].

In addition, STOMP provided approximately equivalent GC performance and safety as STAR, while also largely reducing the clinical workload (12.7 vs. 10.0 and 8.4 measures/day). This large reduction in the number of measures required per day is likely due to long prediction horizon (N=6) used with STOMP enabling better foresight of treatment options offered, encouraging long term BG goals of the controller. This behaviour is well illustrated in Fig. 9.5, with STOMP offering more gradual changes in nutrition and insulin compared to STAR's relatively rapid changes. Hence, STOMP was able to maintain excellent GC performance and safety, while offering the hour longer 4 hour measurement intervals and, as a result, reducing clinical staff GC workload by approximately 35%, which is critical to clinical uptake and compliance [101], [151], [272].

Interesting to note, in Fig. 9.5, STOMP allowed the predicted $5^{th}$ percentile BG to go below 4.0 mmol/L. This is likely due to the earlier BG prediction costs (1 and 2 hour) being outweighed by other factors such as more desirable future BG predictions (4, 5, and 6 hour) and their associated interventions. Emphasising how STOMP's intervention cost calculation, Eq. (9.7), weights the long term outcome of interventions higher than the immediate predicted BG response. STAR is unable provide this type of behaviour. As a result, STOMP is able to provide more effective GC, especially for patients whose wide prediction bounds, and immediate predicted BG response limit the treatment options able to be offered by STAR.

The method of combining MPC with the stochastic prediction behaviour used by STAR to implement a GC protocol has proven very effective. This approach formalizes the STAR GC algorithm, making

optimization easier for different clinical practices and requirements. Using a series of cost functions, to set the behaviour of the controller means modifications to the controller behaviour can be easily made, which thus allows clinical staff or specific ICUs to put a higher priority on any of the desired performance metrics. Clinical staff could choose the weighting for each performance metric, based on the specific patient's condition or local practice, making the protocol more patient-specific or hospital-specific. For example, if a patient was hyperglycaemic, but the clinicians wanted to continue giving the patient a high amount of nutrition, the cost functions could be adapted so there was a larger penalty for having low nutrition. Thus, the controller would have to choose an intervention with a higher nutrition input, while also trying to maintain a desirable BG.

Additional cost functions, based on other aspects of GC, could also be easily added to STOMP. This level of flexibility is not currently available with the STAR protocol. For example, adding a cost function to reduce large changes in insulin interventions would make the controller less likely to over respond and suit a more cautious clinical practice. The MPC cost functions enabled this added flexibility in implementing a stochastic-predictive controller. Therefore, STOMP is potentially better suited for a more diverse range of clinical practice cultures and cohort-specific approaches than STAR.

It is important to note this MPC form of STAR is different from other MPC GC protocols [214], [232], [297]–[301]. Beyond a different model, STOMP uses stochastic model forecasting [145], [149] to manage intra-patient metabolic variability and risk [123], [124]. In contrast, these other MPC GC protocols commonly use auto-regressive models that are more patient-specific but require more data to adapt to changes, and do not manage variability in any way. As a result, STOMP's MPC approach , as with STAR, can safely predict further ahead because it does not rely on external black- or grey- box machine learning models to manage intra-patient variability.

Virtual trials have been shown to give a good indication of expected clinical performance [230], [295] and be generalizable across ICUs [154]. However, they do not allow for unforeseen clinical exceptions. Therefore, the results only represent an *'ideal'* situation and remain to be confirmed. A clinical pilot trial should be undertaken to validate these results on real patients prior to full clinical

implementation. However, the virtual in-silico design analysis presented has improved the likelihood of a successful clinical implementation. Note, the STOMP controller is currently in development for a clinical trial implementation.

## 9.5 Summary

An MPC GC protocol was developed and optimised for GC in the adult ICU using virtual trials. The STOMP protocol was designed as a model-predictive evolution of STAR, permitting the controller response to be easily tuned to specific, clinically relevant, performance metrics. It has the additional benefit of formalising the heuristic control algorithm of STAR, and providing a much more generalisable approach. The results indicate STOMP retains the performance and safety of STAR, spending approximately 87% of time in the 4.4-8.0 mmol/L BG band and 0.06% of time BG $< 2.2$ mmol/L, while considerably reducing clinical workload, requiring 35% fewer BG measurements. The GC performance and reduced workload of STOMP can be largely attributed to the 6 hour prediction horizon used, giving the controller better foresight into the interventions given. Overall, the STOMP protocol is a promising to development to the STAR protocol, enabling easy customization to a more diverse range of clinical practice cultures, cohort-specific approaches, and patient-specific conditions.

Overall, the virtual trial results of STOMP show the clinical flexibility of STAR has been considerably improved. However, a clinical pilot trial should be undertaken to confirm the results of this study. The combination of MPC and stochastic prediction presented in this chapter is a unique and effective GC methodology, which could be adapted to multiple scenarios.

# Part III:

# Development of the ICING model for Type 2 diabetic ward patients

Three points determine a curve.

David Akin

# Chapter 10

# Design of an interventional subcutaneous insulin trial

## 10.1 Background

Currently in NZ, the initial suggested treatment of type 2 diabetes is generally a significant change in lifestyle (diet and exercise) to try and lower the individual's $HbA_{1c}$ concentration [162], [181]. An $HbA_{1c}$ measurement provides a weighted measure of the mean BG over the previous 120 days [174]. If the targeted $HbA_{1c}$ is not met after 3 months, assistive oral medication is recommended. The initial recommended medication is Metformin (Apotex NZ Ltd., New Zealand) [186]. Metformin acts by increasing the biological efficiency of available insulin, increasing glucose uptake and effectively increasing a patient's sensitivity to insulin [181], [187] and has been proven effective in improving patient outcomes [188]. If the individual's condition still deteriorates they are prescribed Sulphonylurea [186], which acts as a steroid to increase pancreatic insulin output, increasing endogenous insulin secretion [181], [189]. However, it has been shown that 9 years after the prescription of sulphonylurea, approximately 80% of patients will still require insulin treatment [25], [190], where insulin is currently considered the last available treatment option [183], [186], [191].

Many studies have discussed and compared the treatment options for type 2 diabetes, specifically with regard to GC and beta cell degradation leading to reduced endogenous insulin secretion. It has

been shown in many cases that insulin treatment is more effective in preserving beta cells [25], [168], [195], [196], improving lipid metabolism [197]–[200], and achieving GC targets [25], [164], [190], [201] compared to other offered treatments. This result may be due to those receiving oral medication still requiring relatively high endogenous insulin secretion rates from the pancreas, leading to the eventual *'fatigue'* of the pancreas [161], [202]–[205]. Therefore, treating type 2 diabetes with basal insulin, much earlier, may allow the pancreas to *'rest'*, reducing endogenous insulin secretion [206], [207], between meals and thus allowing it to act more appropriately during meals [208]. Ultimately, this approach suggests 'early' basal insulin therapy may improve GC and reduce the degradation of an individual's pancreatic functionality. However, if basal insulin suppresses endogenous insulin secretion entirely, including when patient's have meals, or has no effect on endogenous insulin secretion very limited benefit will be observed. As there is limited literature available in this area a clinical trial is needed to test the potential benefits of basal insulin therapy.

Although basal insulin therapy may have potential benefits, it increases the risk of hypoglycaemia if not taken correctly [64], [66], [164], [180], [201], [209]–[211]. Use of insulin is thus avoided clinically due to human variability [124] making dosing riskier [191], [201]. In addition, there is also a negative stigma around starting insulin therapy, as individuals and the physician feel they have failed [183]. Therefore, before early basal insulin therapy can be offered, a very safe and effective dosing protocol needs to be developed. Only then can any potential benefits of early basal insulin therapy be realized.

The trial designed in this chapter investigates the idea of insulin being used as an initial treatment option for type 2 diabetics. Specifically, whether or not basal insulin supports or suppresses endogenous insulin production and improves GC. In addition, the data gathered from this trial will allow a comprehensive insulin-glucose model to be developed for the type 2 diabetes cohort.

## 10.2 Aims

**Primary aims:**

- Determine if basal insulin supports or suppresses endogenous insulin secretion.
- Gather data to develop a model of a type 2 diabetic and pre-diabetic patient's insulin-glucose response, with and without exogenous basal insulin support.

**Secondary aims:**

- Determine the inter-patient variability in the appearance kinetics of the basal insulin analog Detemir (Levemir, Novo Nordisk, Bagsvaerd, Denmark).
- Determine if basal insulin support improves a patient's endogenous GC.

## 10.3 Study design

Non-randomised, uncontrolled pilot trial investigating the effects of subcutaneous basal insulin treatment for people with type 2 diabetes and pre-diabetes.

### 10.3.1 Patient overview

Patients receiving elective cardiac surgery are targeted because they have a high chance of meeting the type 2 diabetic or pre-diabetic eligibility criteria of this study [165], [167] and commonly stay 2-3 days in the ward, post-surgery, for recovery. The typical cardiac surgery patients time-line at St George's Hospital in relation to the trial can be seen in Fig. 10.1.

#### *10.3.1.1 Locality*

The trial will be undertaken at the Sir George Seymour Ward of St George's Hospital, Christchurch, NZ.

#### *10.3.1.2 Entry criteria*

Cardiac surgery patients who are considered to have type 2 diabetes or pre-diabetes ($HbA_{1c} > 40$ mmol/mol or $> 5.8\%$, and fasting BG $> 6.0$ mmol/L [173]), and have an expected length of stay in the Sir George Seymour Ward equal to or greater than 2 complete days.

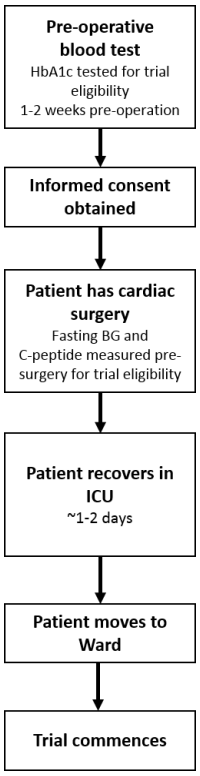



Figure 10.1: Flow chart of patient time-line from eligibility test to commencement of the trial at St George's Hospital, New Zealand.

#### *10.3.1.3 Exclusion criteria*

Patients $< 18$ years of age; Inability to gain consent; Lack of equipoise (for any reason) on the part of the treating clinician.

#### *10.3.1.4 Informed consent*

All patients who are receiving cardiac surgery at St George's Hospital will be provided with a trial information sheet in their pre-surgery information packs. Written, informed consent will be obtained from eligible patients by Dr. Geoff Shaw or the Intensivist on at St George's either in the morning or night before the patient's cardiac surgery. Patients can withdraw from the study at any time. However, if a basal insulin dose has been given within the last 24 hours the patients BG will need to be monitored relatively strictly (approximately every 3 hours). Should a patient be withdrawn during the trial, consent will be sought after to use any data collected up to that point in time, otherwise it will be destroyed.

### 10.3.2 Trial protocol

The trial commences the morning after the patient has moved from the ICU to Sir George Seymour Ward, approximately 44 hours on average after surgery. For the next 2 complete days measurements for the trial are taken around the patient's meals. Patient demographic data, such as age, weight, height, gender, and patients prior diabetes related history will be recorded once consent is received.

#### *10.3.2.1 Meal monitoring*

Before and after each patient's meal (Breakfast, Lunch, and Dinner), 4.0 mL blood samples are taken to measure BG, plasma insulin, and C-peptide concentrations. C-peptide concentrations are used to estimate the patients endogenous insulin secretion rate, per Section 11.2.2.1. The 4 blood samples taken around each patient's meal are shown in Fig. 10.2.

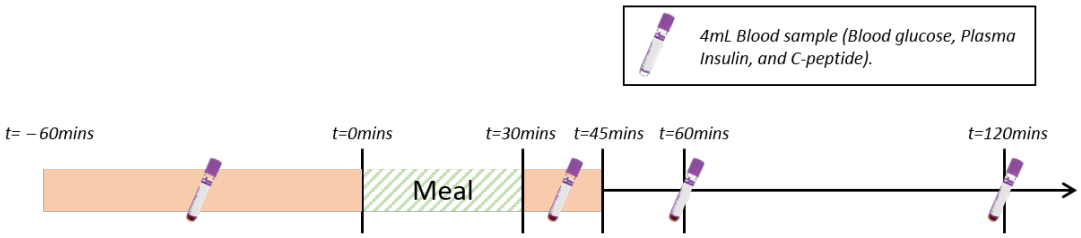



Figure 10.2: Blood sampling time-line around each patient's meal. The shaded orange region indicates the region in time where the measurement can be taken.The dashed green region indicates the time in which the patient has the meal tray.

The measurement prior to each meal is designed to capture the patient's initial state before a meal. This state is assumed to be relatively constant if no food has been consumed in the past 3 hours, as illustrated in Fig. 10.3. The 2 measurements immediately post-meal are designed to capture the patient's response around the postprandial peak in BG and plasma insulin, as illustrated in Fig. 10.3. The final measurement is designed to capture the standard 2 hour postprandial BG and plasma insulin level in the second phase of typical response [303]. The timing of all 4 measurements are compared to the BG and plasma insulin levels published in Jacobs et al. [236] for hospitalised non-diabetic subjects, as illustrated in Fig. 10.3.

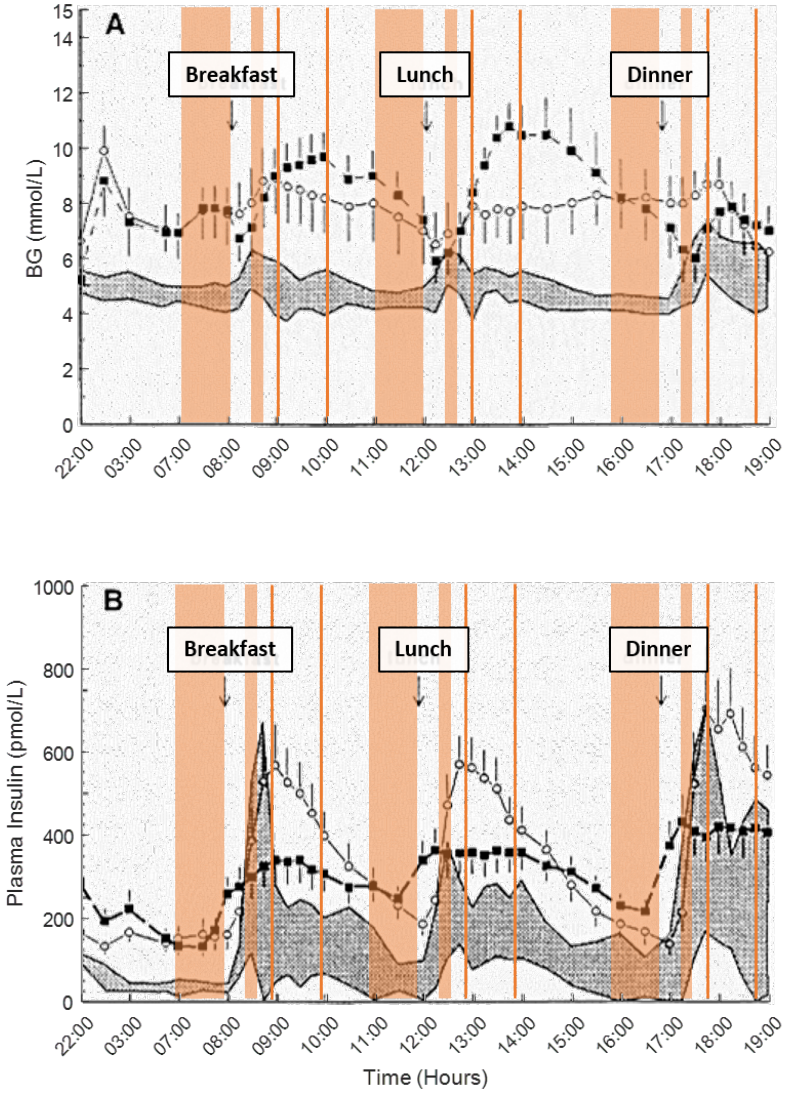



Figure 10.3: The proposed blood sampling time-line (orange region) in comparison to a modified plot from Jacobs et al. [236]. Mean ± standard error (SE) of blood glucose (BG) and plasma insulin measurements for hospitalised for non-diabetic subjects (Shaded area), and mean ± standard deviation (SD) of blood glucose (BG) and plasma insulin measurements for hospitalised diabetic patients treated with lispro (-◯-) and human insulin (-■-) are shown.

#### *10.3.2.2 Insulin treatment allocation*

Patients are split evenly between one of two streams for insulin treatment. Stream A will be conducted on the first half of patients (5 patients), and Stream B will be conducted on the remaining half of patients (5 patients).

**Stream A:** Trial Day 1 patient receives a small basal insulin dose in the morning.

Trial Day 2 patient does NOT receive any insulin.

**Stream B:** Trial Day 1 patient does NOT receive any insulin.

Trial Day 2 patient receives a small basal insulin dose in the morning.

Measurements are the same for both streams, only the timing of the basal insulin dose varies. Two streams of insulin dose timing are used to eliminate the scenarios associated with differing patient response. These scenarios are:

- The patient is more stressed, post-cardiac surgery, on day 1 compared to day 2. As a result, the patient may have more stress hormones present on day 1, *naturally* raising BG [39], [85]–[88], suppressing endogenous insulin secretion [74], [84], and thus conflicting with the potential influence of basal insulin therapy. Therefore, giving the insulin dose on day 2 should minimise this influence.
- The benefits of basal insulin support may not occur immediately and require a period for the body to adjust to the external insulin intervention. Therefore, giving the insulin dose on day 1 should be able to observe this effect.

Hence, having two streams of insulin treatment, one on day 1 and one on day 2 of ward stay, post-cardiac surgery, allows for both scenarios to be observed.

#### *10.3.2.3 Insulin Dosing*

Levemir (Insulin Detemir analog) from 100 U/mL Levemir FlexTouch pens (Novo Nordisk, Bagsvaerd, Denmark) is used. Insulin is injected in the lower abdomen, in the morning during the first blood sample of the day. Insulin is very conservatively dosed based on the patient's Total Daily Dose (TDD) insulin requirements [304], as defined:

$$\begin{gathered} TDD = 0.5 \times BW \\ Basal/Background\ dose = 50\%\ of\ TDD \\ \therefore Dose\ size = 0.25\ U/kg/day \end{gathered} \tag{10.1}$$

Where: $TDD$ = Total Daily Dose ($U/day$), $BW$ = Body wieght ($kg$)

For example, an 80 kg patient would receive:

$$Basal\ insulin\ dose = 0.25 \times 80 = 22\ U/day$$

### 10.3.3 Sample size

As this trial is an investigative pilot trial, only 10 patients will be included in this trial. This sample size will provide enough data to address the trial's primary and secondary aims. More specifically, this sample size does not provide enough data/power to assess patient outcomes. However, assessing patient outcomes is not the aim of this first trial.

A total of 10 participants will be recruited. However, if one or more patients do not complete both trial days, either because they have withdrawn or because they were unable to complete the study, additional patients will be recruited until 5 patients in each stream have completed both days of the study.

### 10.3.4 Clinical surveillance

#### *10.3.4.1 Blood sampling*

At each measurement point, a 4.0 mL whole blood sample will be taken from the patient's peripheral IV line. The one blood sample is used for assessment of BG, C-peptide, and plasma insulin. BG tests will be performed in-situ with an Optium Neo H (Abbott Diabetes Care, Illinois, USA) PoC BG meter, using approximately 0.1 mL of the IV blood sample. C-peptide and plasma insulin will be determined by immunometric assays (Elecsys 2010, Roche Diagnostics, Germany) at Canterbury Health Laboratories (CHL). Only one 4.0 mL blood sample per measurement is used to minimise daily blood draw from the patient. With 12 blood samples a day the total expected blood draw, per day, for each patient is 48 mL.

#### *10.3.4.2 Continuous glucose monitoring (CGM)*

Two iPro2 continuous glucose monitor (CGM) sensors (Medtronic, MiniMed, Northridge, CA, USA) will be inserted for retrospective analysis of BG data, enabling assessment of higher frequency BG dynamics. The CGMs will be inserted into the patient's lower abdomen by a member of the research team or a trained clinician, preferably while the patient is in the ICU post-cardiac surgery, but no later than 12 hours before initiation of the trial to allow calibration of the sensor [305]. The CGMs will be removed the morning after the trial has concluded. The sensor site will be monitored frequently by the nursing staff for signs of possible infection or pressure trauma, and the sensors will be removed if there are any concerns.

#### *10.3.4.3 Nutrition details*

For every meal the patient consumes the nutritional information will be recorded. The amount and type of food consumed will be estimated from meal tray photos pre- and post- meal. The total nutritional content of each meal is provided by the St George's Hospital Kitchen. External food brought will be discouraged, but similarly monitored if consumed.

### 10.3.5 Adverse Events

All adverse events will be reported to nursing staff and the research team. Specifically:

**Hypoglycaemia:** In the rare event the patient experiences mild hypoglycaemia (BG $< 4.0$ mmol/L), the patient is given an oral 15 g dose of dextrose. The patient's BG is then checked approximately 20 minutes later to see if it is $> 5.0$ mmol/L [306]. If not, the patient will be given another 15 g dose of dextrose until their BG is measured to be $> 5.0$ mmol/L.

**Hyperglycaemia:** If 2 consecutive BG are measured $> 10.0$ mmol/L, the patient may be treated with a small bolus of IV rapid acting insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark), as per standard practice.

**Post-cardiac surgery complications:** If complications arise due to the cardiac surgery, unrelated to the trial, such as cardiac arrhythmia, the patient will be treated as per standard practice. Note, this may involve IV infusion of anti-arrhythmic drugs such as Amiodarone Hydrochloride which is administered with a 5% glucose solution [307]. If more severe complications arise, such as large internal bleeding requiring resternotomy and tamponade, continuation of the trial will be up to the clinicians discretion.

If either hyper- or hypo- glycaemia occurs the patient will not be excluded from the study and normal trial procedure will continue. However, patients are able to opt out of the trial at any time if they feel uncomfortable.

#### *10.3.5.1 Compensation*

Participants in will be covered by the Accident Compensation Corporation (ACC) of NZ should any harm occur from trial participation.

### 10.3.6 Data Management

Every patient will be assigned a unique study number. All data will be collected using specific case report forms labelled with the allocated study number. Collected data will be entered into a secure database. All records will be secured in a locked drawer or password-protected computer database.

### 10.3.7 Trial Identification

The trial is reviewed and approved with the Southern Health and Disability Ethics Committee (HDEC). Ref: 16/STH/152, 26th September 2016.

## 10.4 Discussion

It has been shown if type 2 diabetes is treated early and *'effectively'*, its progression can be stopped and normo-glycaemia maintained [176]–[178], reducing the associated long term health care costs. However, if not treated effectively, the individual's condition may completely degrade, secreting only negligible amounts of endogenous insulin. At this point their condition becomes very similar to an individual with type 1 diabetes in terms of treatment [179]–[181], where such treatment is difficult, costly, and often not robust. As a result, complications and thus costs mount rapidly.

Insulin therapy for type 2 diabetes usually begins with basal insulin support [179]–[181], where basal insulin is a subcutaneous long acting analogue of insulin which is designed to be released slowly and steadily into the blood stream over a long period of time (typically 16+ hours). The most common commercially available forms of long acting insulin are Glargine and Detemir. Basal insulin support is designed to mimic the normal basal insulin production of the pancreas [179]–[181], [183], leaving the pancreas free to act around meals. The most common dosing regime is a sliding scale proportional to the individual's morning fasted BG week long average [180], [192], [193]. However, if an individual's condition deteriorates even further they are prescribed both basal and rapid acting insulin to try and mimic the entire functionality of the pancreas [179]–[181], [183], similar to type 1 diabetes treatment [183], [194].

Problematically, current approaches to care mean basal insulin therapy is usually only offered after an individual with type 2 diabetes condition has substantially progressed, and beta cell endogenous insulin production is likely significantly depleted [176]. This approach is taken largely due to the perception that the trade-off in care quality is out weighed by the significant risks associated with insulin therapy [64], [66], [164], [180], [201], [209]–[211]. Therefore, paradoxically, starting basal insulin therapy this late in the progression of type 2 diabetes may not allow the potential benefits of insulin therapy to be best utilised.

One study in particular looked at prescribing people age 50 and over, with evidence of cardiovascular disease and newly detected or established diabetes (pre-diabetes or early stage type 2 diabetes), with standard practice diabetes treatment or one daily injection of Glargine (basal insulin) for 6 years [212]. The primary outcomes were in regard to cardiovascular events, and no conclusive outcome was found. However, a 41% reduction in the number of people with newly diagnosed diabetes was seen in the group which used basal insulin therapy compared to those who were receiving standard treatment [193], despite having significant numbers who quit this therapy or were not fully compliant. This outcome strongly emphasises the potential benefits of early basal insulin therapy, which is otherwise not used clinically, as well as the risks, difficulty, and resulting non-compliance seen when using this therapy with current dosing protocols and technology.

Hence, because the progression of type 2 diabetes can be slowed or stopped, preventative treatment is the focus of this study. In particular, this study is designed to observe the effect of intervening with basal insulin therapy very early on in the development of type 2 diabetes. The data gathered from this trial will help us better understand an individual's response to basal insulin therapy and determine if it is viable preventative treatment option for people with type 2 diabetes. In particular, it will provide the data to enable the development models accurate enough for safe and effective BG control.

## 10.5 Summary

Previous literature has highlighted the potential benefits for early basal insulin therapy as an preventative treatment for individuals with type 2 diabetes. In particular, in regard to preservation of endogenous insulin secretion and improved GC. However, limited literature exists around whether or not basal insulin therapy supports or suppresses endogenous insulin secretion. The proposed trial aims to gather data to investigate the affect of basal insulin therapy on endogenous insulin secretion, and develop a model to help us better understand and eventually safely, and effectively control the type 2 diabetes cohort.

If the data from this trial shows basal insulin therapy to be a potentially viable preventative treatment for type 2 diabetes, it could provide a relatively safe and effective way of reducing/stopping the progression of type 2 diabetes.

# Chapter 11

# Initial results of an interventional subcutaneous insulin trial

## 11.1 Background

In Chapter 10, an interventional subcutaneous insulin trial was designed to investigate the idea of using insulin as an initial treatment option for type 2 diabetics. The trial specifically looks at whether or not basal insulin supports or suppresses endogenous insulin production and thus if it can improve GC in early type 2 diabetes or pre-diabetes. The data gathered from this trial will also allow a comprehensive insulin-glucose model to be developed for the out-patient type 2 diabetic and pre-diabetic cohort.

The trial was designed and ethics granted in September 2016. Once nursing was arranged with St Georges Hospital, the first patient was enrolled in March 2017. However, after this patient completed the trial a few issues arose about the trial workload for the St George's Hospital nursing staff. As a result, external research nurses were required to be organised before the trial could be continued. Therefore, the next trial patient was delayed until December 2017. This chapter provides the initial results and raw data analysis of the first two patients enrolled in the trial.

## 11.2 Methods

### 11.2.1 Patient Demographics

Two patients have currently been enrolled in this study. Patient 1 had no prior history of diabetes and Patient 2 was a well controlled type 2 diabetic. The patient demographics can be seen in Table 11.1. Notably, their $HbA_{1c}$ levels are similar and are just within the currently considered pre-diabetic status for NZ (40-50 mmol/mol) [173].

Table 11.1: Demographic data for the two trial patients who have completed the study.

| Patient Trial ID | 1 | 2 |
|---|---|---|
| Age | 73 | 74 |
| Gender | Male | Female |
| Weight (kg) | 88 | 72 |
| Height (cm) | 180 | 163 |
| HbA1c (mmol/mol) | 41 | 43 |
| Prior History of Diabetes | No | Yes, 10 years on Metformin |

### 11.2.2 Raw Measurement Analysis

*11.2.2.1 Endogenous insulin secretion*

Plasma insulin and C-peptide is measured from whole blood samples 4 times around each meal the patient receives. By using the population parameters and pharmaco-kinetic model described by Van Cauter et al. [308] endogenous insulin secretion rates can be deconvolved from the measured C-peptide data. The pharmaco-kinetic model presented in Van Cauter et al. [308] can be seen in Eqs. (11.1) and (11.2).

$$\frac{dC(t)}{dt} = U_{en}(t) - (k_1 + k_3) \times C(t) + k_2 \times Y(t) \tag{11.1}$$

$$\frac{dY(t)}{dt} = k_1 \times C(t) - k_2 \times Y(t) \tag{11.2}$$

Where: $C$ = C-peptide in central compartment (pmol/L)

$Y$ = C-peptide in peripheral compartment (pmol/L)

$U_{en}(t)$ = Endogenous insulin secretion rate (pmol/min)

Given the Van Cauter et al. [308] dynamic parameters:

$$k_2 = \frac{-(A \times b + B \times a)}{A + B} \tag{11.3}$$

$$k_3 = \frac{a \times b}{k_2} \tag{11.4}$$

$$k_1 = -a - b - k_2 - k_3 \tag{11.5}$$

Where:

$$a = \frac{log(2)}{ShortHalfLife} \tag{11.6}$$

$$b = \frac{log(2)}{LongHalfLife} \tag{11.7}$$

$$Fraction = \frac{A}{A + B} \tag{11.8}$$

And substituting Eq. (11.8) into Eq. (11.3) gives:

$$k_2 = Fraction \times (b - a) + a \tag{11.9}$$

Given this information each of the kinetic patient-specific parameters ($k_1, k_2, k_3$, and Volume of distribution) can be derived from Table 11.2 and Equations (11.10) to (11.12).

Table 11.2: Van Cauter et al. population parameters [308].

| | Normal | Obese | NIDDM |
|---|---|---|---|
| Short half-life (min) | 4.95 | 4.55 | 4.52 |
| Fraction | 0.76 | 0.78 | 0.78 |

*Non-insulin dependent diabetes mellitus (NIDDM)

$$LongHalfLife = 0.14 \times Age + 29.2 \tag{11.10}$$

$$Vol.\ Distribution = \begin{cases} Male & 1.11 \times (BSA) + 2.04 \\ Female & 1.92 \times (BSA) + 0.64 \end{cases} \tag{11.11}$$

As body surface area (BSA) was not measured it was estimated using Eq. (11.12) from [309].

$$BSA_{estimate}(m^2) = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}} \tag{11.12}$$

By using discrete deconvolution of Eqs. (11.1) and (11.2) the endogenous insulin secretion rate, $U_{en}$, can be solved for, Eq. (11.13). Tikhonov 2nd order regulation [310] was used with a $\lambda = 50$, estimated by the L-curve approach [311], to ensure a smooth solution of endogenous insulin secretion rate was found, restricting non-physiological stepwise jumps in $U_{en}$.

$$U_{en}(t) = (X^T X + (\lambda L_2)^T (\lambda L_2))^{-1} X^T (C_{imp} - C_{init}) \tag{11.13}$$

Where: $U_{en}(t)$ = Endogenous insulin secretion rate (pmol/min), $X$ = Toeplitz matrix of $C_{imp}$

$\lambda$ = Regularization factor (=50), $L_2$ = 2nd order regularisation matrix:

$$L_2 = \begin{bmatrix} 1 & -2 & 1 & & & \\ & \ddots & \ddots & \ddots & & \\ & & \ddots & \ddots & \ddots & \\ & & & 1 & -2 & 1 \end{bmatrix}$$

$C_{imp}$ = Impulse response of Van Cauter Eqns, as seen in Fig. 11.1.

$C_{init}$ = Initial condition response of Van Cauter Eqns, defined by Eqs. (11.14) and (11.15) [308].

$$C(t_0) = C_{meas}(t_0) \tag{11.14}$$

$$Y(t_0) = C_{meas}(t_0) \times \frac{k_1}{k_2} \tag{11.15}$$

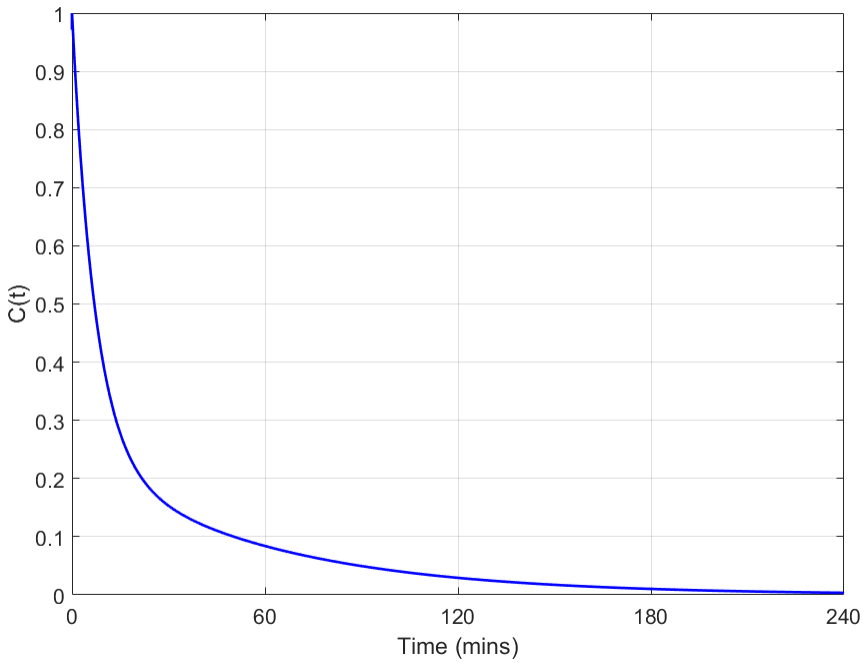



Figure 11.1: Impulse response of Van Cauter et al. [308] endogenous insulin secretion model equations.

#### *11.2.2.2 CGM Retrospective Calibration*

Two CGM sensors were inserted into the abdomen of each patient to provide retrospective information of BG trends. Two CGMs were inserted to increase the reliability of the observed trend. Retrospective calibration was performed by forcing the raw signal received from each CGM sensor through each of the measured BG points. This recalibration ensured the CGM signal captured the BG measurements, while still giving an indication of intermediate trends in BG.

#### *11.2.2.3 Meal monitoring*

Patient meals were monitored by recording the time a patient was given a meal tray and the time the meal tray was taken back. Photos were taken at each of these times to allow an estimation of initial meal size and the proportions of each part of the meal the patient consumed. Nutritional information given by the packaged food or St George's kitchen was used to estimate the macro nutrients of each meal (Energy, Protein, Carbohydrates, Sugar, Fibre, Fat, and Saturated Fat). An example of the photos taken before and after each meal can be seen in Fig. 11.2. For lack of better knowledge, all meals were assumed to be consumed equally over the entire period in which the patient had the meal tray. Any other snack food brought in was also monitored.

(a) Pre-Lunch (b) Post-Lunch

Figure 11.2: Example of meal photos taken pre and post each meal used to estimate the amount of each food type consumed.

## 11.3 Results

Each of the patient's fasted pre-surgery measurements are shown in Tables 11.3 and 11.4. Notably Patient 2, the established type 2 diabetic, had a much higher fasted C-peptide and plasma insulin level, suggesting the pancreatic *'stress'* mentioned in Chapter 10. The measurements taken throughout each of patient's trial days are presented in Figs. 11.3 and 11.4, where the endogenous insulin secretion rate is derived from the C-peptide measurements, as described in Section 11.2.2.1. Note, although all of the macro nutrients were recorded, as stated in Section 11.2.2.3, only carbohydrates are presented to aid clarity of the figures. Table 11.5 shows there is slight differences between the day the patient received basal insulin and the day they did not. However, normalisation of these values to account for meal size and its macro nutrients is required before any relationships can be observed.

Table 11.3: Patient 1 fasted pre-surgery measurements.

| BG (mmol/L) | C-peptide (pmol/L) | Plasma insulin (pmol/L) |
|---|---|---|
| 7.8 | 771 | 54 |

Table 11.4: Patient 2 fasted pre-surgery measurements.

| BG (mmol/L) | C-peptide (pmol/L) | Plasma insulin (pmol/L) |
|---|---|---|
| 7.2 | 1370 | 131 |

Table 11.5: Comparison of the maximum recorded blood glucose (BG), endogenous insulin secretion ($U_{en}$), and plasma insulin ($U_{plasma}$) on each of the trial days, with and without basal insulin support. Both patients were in Stream A.

| | Insulin day maximum values | | | Non-insulin day maximum values | | |
|---|---|---|---|---|---|---|
| | BG (mmol/L) | $U_{en}$ (mU/hr) | $U_{plasma}$ (mU/L) | BG (mmol/L) | $U_{en}$ (mU/hr) | $U_{plasma}$ (mU/L) |
| Patient 1 | 9.8 | 229 | 229 | 10.5 | 250 | 142 |
| Patient 2 | 13.6 | 261 | 263 | 13.3 | 317 | 269 |

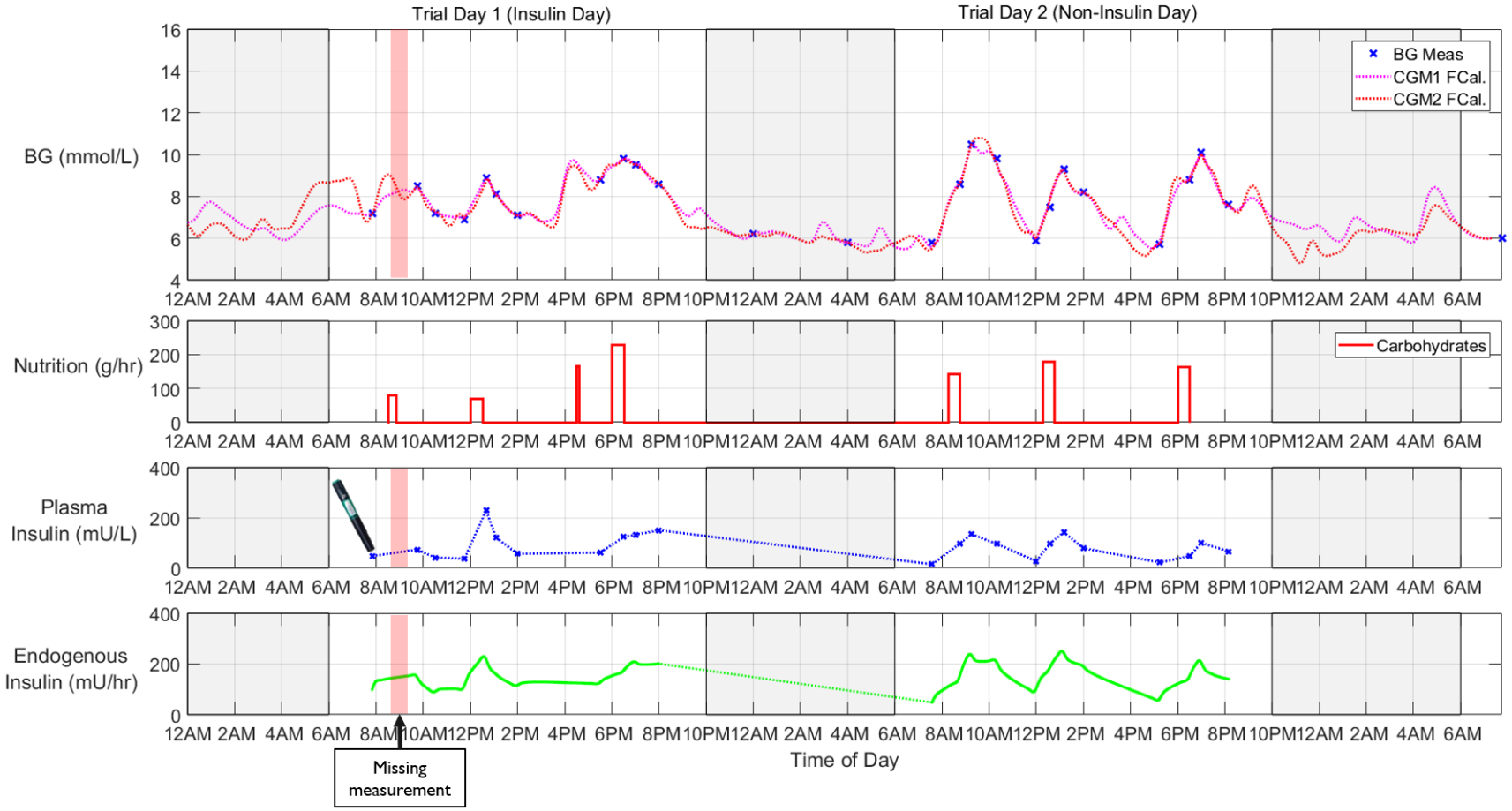



Figure 11.3: Summary of the data collected from Patient 1. Insulin given on Day 1 (Stream A).

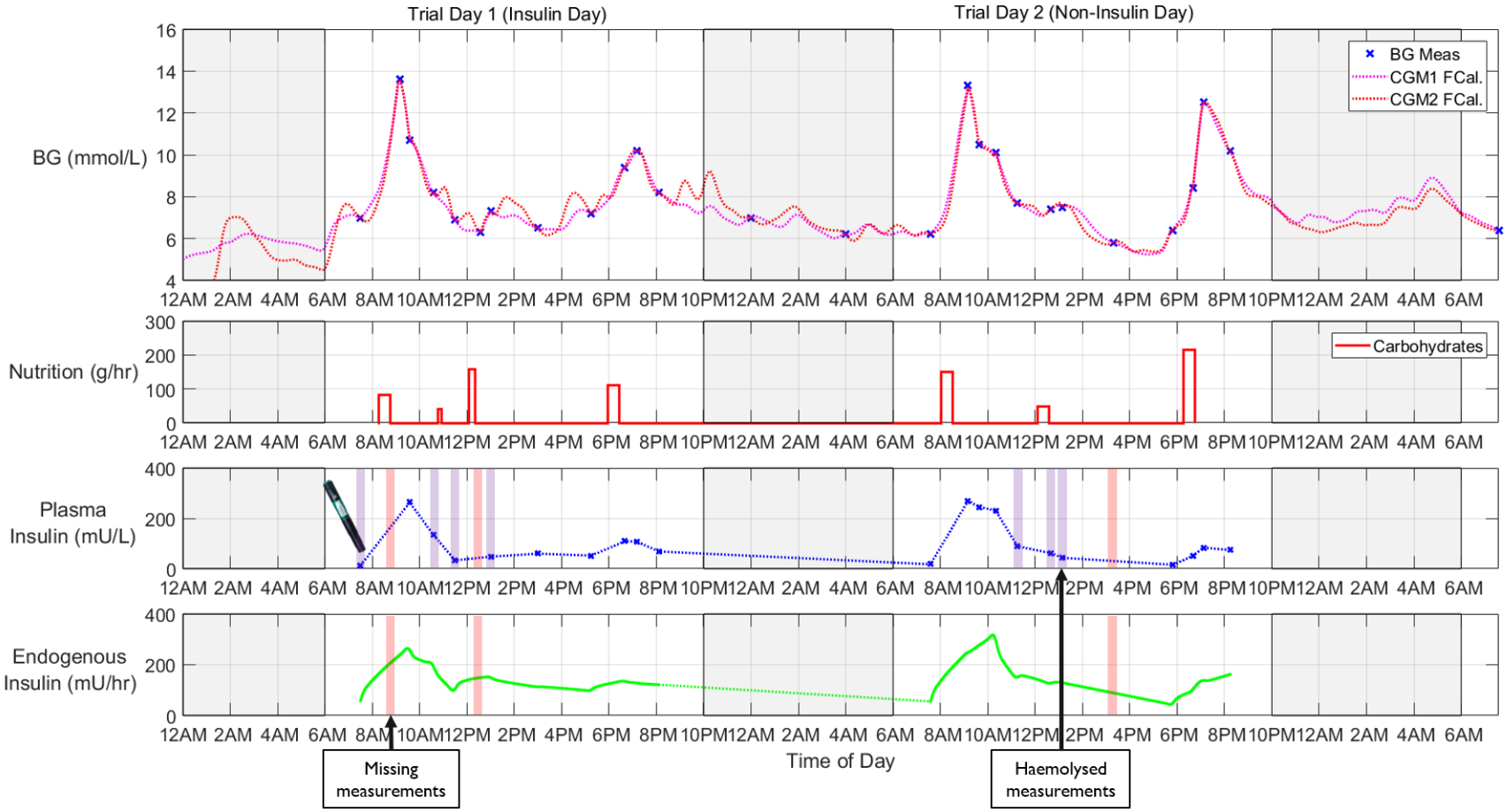



Figure 11.4: Summary of the data collected from Patient 2. Insulin given on Day 1 (Stream A).

## 11.4 Discussion

After the first patient enrolled in this study issues arose around nurse workload. For the first patient, trial blood samples were taken by the nurse who was also caring for the patient. This resulted in an unmanageable workload for this nurse, especially during the morning routine (showering, walking, cardiogram etc.). In addition, BG measurements were taken using a hand-held iSTAT blood gas analyser (Abbott Point of Care Inc., Princeton, NJ, America), which required special nurse training. Overall, these issues resulted in external research nurses being needed, and the replacement of the hand-held iSTAT blood gas analyser with a standard PoC meter, Accu-Chek Performa II (Roche Diabetes Care Inc., IN, America), compromising on BG measurement accuracy.

Once these changes were made, prior to Patient 2, the trial appeared to be considerably more clinically feasible in terms of nurse workload. No major concerns of patient discomfort or safety arose for either patient. Only minor discomfort from the multiple peripheral IV line blood samples was reported. No issues arose due to the subcutaneous insulin injection and/or dose given.

The measurements of BG, plasma insulin and C-peptide appear to capture a patients typical meal response very well, approximately capturing the peak and postprandial decay in BG, plasma insulin and endogenous insulin production, as seen in Figs. 11.3 and 11.4. This peak and postprandial decay response is especially prominent during lunch on trial day 2 of patient 1, Fig. 11.3, and during breakfast on trial day 2 of patient 2,Fig. 11.4. Therefore, the timing of measurements appears to capture the desired meal response characteristics.

A common issue during both trial patients was the inability to draw blood from the peripheral IV line. As blood was sampled frequently from the peripheral IV line, commonly in the dorsal vein (Hand), irritation (Phlebitis) and aspiration resulting in the collapsing of the vein commonly occurred. When these issues occurred a new IV line was required to be inserted, discomforting the patient and in some instances resulting in no blood sample being taken. In Patient 1, the IV line was replaced 2 times, and 4 times in Patient 2. It has been presented in many cases that the use of peripheral IV lines for frequent and prolonged blood sampling can result in increased complications

[312]–[314]. Therefore, if possible, keeping the patient's central venous line in post surgery should be considered for future patients, as these lines are more suitable for frequent and prolonged blood sampling [312].

A prominent difference between the patients was the number of haemolysed blood samples in Patient 2. Haemolysis occurs due to the release of haemoglobin and other intracellular components from red blood cells into the plasma, and, as result, the plasma insulin assays give a lower reading than what was actually present. Haemolysis can be caused by any process in which the red blood cells could be damaged. Possible areas where haemolysis could have occurred in this study are:

- Syringe collection of blood exerting pressure on the red blood cells and damaging them.
- Collection through an IV catheter rather than a straight needle.
- Excessive tube shaking damaging the red blood cells.
- A too smaller gauge catheter was used damaging red blood cells on entry to the catheter.
- The blood samples not kept cold enough denaturing the red blood cells.

All of these issues are potentially viable reasons for the frequent haemolysis in the second patient. However, due to blood draw being more of an issue in Patient 2 relative to Patient 1, considerably more pressure may have been used to try and draw blood, and, as a result, haemolysis frequently occurred. Again, a central venous line may allow for better blood draw in these situations, particularity when the excessive pressure required to draw the blood results in an unreliable plasma insulin measurement.

Due to frequent missing or unreliable measurements, a method should be developed to recover the underlying meal response. Once all the patient data is collected a generalised meal response wavelet or set of wavelets could be formed to approximate the complete meal responses recorded, potentially using added information from the CGM response. These wavelets could then be fitted to meals where data is missing or unreliable to approximate the entire meal response. This technique could provide an innovative way of recovering the meal response characteristics where data is missing or unreliable.

In contrast to the ICU, where patients are fed relatively constantly throughout the day, patients in the ward are fed commonly 3 times per day, with meals of varying nutritional content. Hence, the modelling of meal dynamics is of relatively high importance in this setting, given the potential trade-offs to $S_I$. In addition, better modelling of the meal responses will help *'normalise'* a patient's response to a given meal, allowing easier inter-meal comparisons.

## 11.5 Summary

An interventional subcutaneous insulin trial was designed in Chapter 10 to investigate the idea of insulin being used as an initial treatment option for type 2 diabetics. The initial results and raw data analysis of the first two patients are presented in this chapter. Issues around nurse workload were identified in the first trial patient, which resulted in the need for external research nurses in future patients. After arranging external research nurses the clinical implementation of the trial appeared to provide a much more manageable workload for everyone involved. No issues around patient discomfort and/or safety arose during either of the patients.

The measurement timing appears to captures the patient's meal response, peak and postprandial decay, well through out the day. However, measurements were sometimes missed due to issues with blood draw from the peripheral IV line. This was a issue common to both patients and could be remedied by the use of a central venous line. In addition, the difficult blood draw from the peripheral IV line in Patient 2 may have resulted in increased occurrence of haemolysis, reducing the reliability of plasma insulin measurements.

# Chapter 12

# Conclusions

It has been shown, in a range of clinical settings, that BG dysregulation is associated with increased complications leading to increased morbidity and mortality. These irregularities may be due to either the influence of stress hormones and external drugs in the critical care setting or a developed resistance/impairment to glucose regulation as seen in type 2 diabetes. In both situations, safe and effective external intervention to assist in regulating BG levels has shown benefit. A method that has proven effective in the ICU is the STAR model-based GC protocol. Therefore, this type of model-based GC may prove effective for out-patients with type 2 diabetes.

The ICU GC protocol STAR is unique in the respect that it is a tablet-based protocol that uses a combination of population-based stochastic models and MPC to provide safe and effective risk-based GC. STAR is developed for the ICU setting, and more specifically the model used, the ICING model, is developed based on ICU patient characteristics. Thus, for a version of the STAR GC protocol to be used in an out-patient setting the model and GC methodology need to be adapted.

The aim of this research was to develop the STAR protocol and associated ICING model for better suitability in out-patient GC. In-silico and clinical data sets were used to review and develop control methodologies and technologies, and their impact on GC and outcomes. In addition, a clinical trial was designed to better understand the metabolic behaviour of type 2 diabetes, to enable improved, and safer control of this cohort. The main research areas and their rationale include:

**Assessment of BG interpolation and resampling** Improve approximations of intermediate BG dynamics in sparse data sets and improve comparison of GC performance statistics, particularly given the sparser out-patient data available.

**Evaluation and simplification of STAR's stochastic model** Determine if patient $S_I$ variability is generalisable across cohorts and if it can be approximated by mathematical functions to simplify risk-based dosing.

**Improving the representation of $S_I$** Create a more physiologically realistic representation of $S_I$ that reduces the influence of erroneous BG measures.

**Review STAR clinical data** Determine GC performance, safety and workload of the STAR protocol in use to assess its strengths and weakness for use with out-patients.

**Assessment of STAR compliance** Determine the validity of recorded STAR information and where areas of compliance could be improved within the protocol, as compliance is a key issue in protocol success.

**Assessment of STAR feeding** Determine if STAR GC influences a patient's ability to receive nutrition in an international context.

**Investigation of simpler STAR nutrition protocols** Determine if the same GC performance and safety can be achieved with a lower workload nutrition protocol, thus also assessing how much GC relies on nutrition control.

**Development of the STOMP GC protocol** Develop a MPC GC protocol which was more clinically flexible, and used longer time frames for determining dose as might be seen in the less acute scenarios.

**Design of subcutaneous basal insulin support trial** Create a trial to investigate the idea of basal insulin support for type 2 diabetics and pre-diabetics.

**Initial results of basal insulin support trial** Present the initial results of the first patients on the trial.

The method of interpolation used to estimate intermediate BG dynamics was investigated. Piece-wise functions and B-spline basis functions (1st and 2nd order) were fitted to clinical BG measurements and their ability to capture removed measurements assessed. Overall a linear piece-wise function performed the best, providing an estimate of intermediate BG dynamics within measurement error. Thus, linear interpolation should be used when approximations are required in modelling and statistical analysis. In addition, the effect of resampling variably sparse BG measurements, common to ICU GC protocols, on GC performance statistics was investigated. A significant difference in key GC performance statistics was found when comparing raw to hourly and/or minutely resampled interpolated BG measurements. Therefore, for fair comparison of a GC protocol's performance, minutely or hourly resampled linear interpolation of raw BG measurements should be performed.

Treatment options offered by STAR are very dependent on the $5^{th}$ and $95^{th}$ percentile $S_I$ bounds defined in the stochastic model used. Therefore, the current stochastic model bounds were evaluated in relation to the stochastic bounds of stochastic models made from 3 independent STAR cohorts (Christchurch (New Zealand), Gyula (Hungary), Kuantan (Malaysia)). The $S_I$ variability seen in both Gyula and Christchurch were well captured by the current STAR controller stochastic model, with the $S_I$ variability being within the controllers current stochastic model bounds consistently equal to or greater than 90% of the time. The $S_I$ variability in the Malaysia cohort was seen to be much larger than the what was in the currently used STAR controller stochastic model, with the $S_I$ variability being within the controllers current stochastic model bounds approximately 65% of the time. However, this discrepancy is likely due to the large non-compliance of data entry in Malaysia and a re-evaluation of the stochastic model is required once compliance is improved. In addition, piece-wise polynomial approximations of the currently used stochastic models were investigated. The GC performance and safety was compared with virtual trials on the STAR Christchurch cohort. The piece-wise polynomials were shown to represent the currently used bounds well (All $R^2$ values $>$ 0.96) and provide approximately equal GC performance (% time in BG band 4.4-8.0 mmol/L, 87.9% vs. 87.5%, P=0.67) and slightly improved safety, having 19 less cases of mild hypoglycaemia (BG $<$

4.0 mmol/L). Overall, the piece-wise polynomial stochastic models provide a promising alternative to the currently used stochastic model.

2nd order B-spline BFs were investigated as an alternative to the current non -physiologically representative zeroth order B-spline (KW = 60) BFs used for $S_I$ identification in the ICING model. Various KW 2nd order B-spline BFs were investigated and compared to the current zeroth order B-spline BF. The BFs were compared in terms physiological relevance, identifiability, robustness to erroneous measurements, and susceptibility to noise. The 180 minute KW 2nd order B-spline BF provided the most physiologically realistic fit to the BG measurements, in both the benchmark cohort and STAR sub-cohort, having very similar fitting error variances to that of the respective BG meter used, whilst showing significantly less susceptibility to erroneous BG measurements. However, the ability for this technique to be directly employed in GC needs further investigation before direct use in the clinical setting.

Clinical data from STAR in Christchurch Hospital ICU, NZ and Kálmán Pándy Hospital ICU, Gyula, Hungary since 2011 was reviewed in terms of GC performance, safety, and generalizability, using the linear interpolation and hourly resampling of BG measures for fair comparison, as investigated earlier. Results of STAR's predecessor, SPRINT, were presented for comparison. Patients on the STAR protocol, in both Christchurch and Gyula, spent over 86% of time on protocol within the targeted 4.4-8.0 mmol/L BG band, with very few occurrences of severe or moderate hypoglycaemia (patients with BG $<$ 2.22 mmol/L, 4/292 Christchurch, and 2/47 Gyula). Thus, showing how the model-based and personalized approach to GC can provide safe and effective GC across differing clinical practices. In addition, in Christchurch STAR outperformed SPRINT by providing higher nutrition, and safe, effective control for all days of stay, while reducing time on protocol and workload, and improving patient safety.

The compliance of the STAR GC protocol in terms of data entry and following STAR's recommendations was investigated. The information recorded by the STAR tablet was compared to bedside sheet information and STAR's recommendations. Data entry and recommendation compliance were both very high, with all intervention having over 86% data entry compliance and approximately 100%

recommendation compliance. In both the data entry and and recommendation compliance, the nutrition interventions (EN and PN) compliance was consistently lower than other interventions. This gap is likely due to either to the difficulty associated with changing the feed rate or clinical circumstances changing the feed rate and STAR not being updated. This analysis supports the argument that STAR is a safe and effective GC protocol which clinical staff trust, and is flexible enough for the clinical environment to allow for very high compliance. However, it also shows that there is still room for improvement in terms of the way in which nutrition interventions are handled.

The STAR GC protocol clinical provision of nutrition to hyperglycaemic patients was compared to the nutrition rates of entire ICU cohorts surveyed in 158 ICUs in Cahill et al. [263]. Mean nutrition rates clinically achieved by the STAR nutrition protocol were significantly higher than the mean and best ICU surveyed, for the first 3 days of ICU stay. Overall, STAR's protocol-driven changes in nutrition rate provide on average nutrition rates for hyperglycaemic patients which are equal to, or better than, the mean of all ICU patients in 158 ICUs from 20 different countries. In addition, the inter- and intra- patient variation of nutritional delivery was assessed in the STAR cohort. Median intra-patient variation was 12.9%, however the IQR of the mean per-patient nutrition rates achieved was 74.3% - 98.2%, suggesting patients do not deviate much from their mean patient-specific nutrition rate and the ability to tolerate glucose intake varies significantly between, rather than within, patients. Therefore, a best nutrition rate is likely patient-specific for patients requiring GC.

Furthermore, the relationship between mean nutrition rate achieved and morbidity, and mortality was investigated. The nutrition rates delivered by STAR showed no association between nutrition delivery to hyperglycaemic patients and morbidity or mortality. However, this analysis was significantly underpowered to asses this relationship. Therefore, it can be inferred the slightly poorer nutrition intervention compliance shown previously should not be the result of STAR feeding too low, but rather the frequency of feed changes.

STAR uniquely maintains normo-glycaemia by changing both insulin and nutrition interventions, and has been proven effective in controlling BG in the ICU. However, most ICU GC protocols only change insulin interventions, making the variable nutrition aspect of STAR less clinically desirable. Three alternative, simpler and lower-workload nutrition protocols were investigated using clinically evaluated virtual trials. The SLQ stepped nutrition protocol considerably reduced workload, improved GC safety, almost halving the number of severe hypoglycaemic cases, while still providing nutrition delivery near equal to the best ICU in an international context. Overall, the SLQ stepped nutrition protocol was the best alternative to the current variable nutrition protocol, reducing workload and making STAR more clinically acceptable. However, a clinical trial should be undertaken to confirm the results of this study.

An MPC GC protocol was developed and optimised for GC in the adult ICU, and potential future use in the out-patient setting, using virtual trials. The STOMP protocol was designed as a model-predictive evolution of STAR, permitting the controller response to be easily tuned to specific, clinically relevant, performance metrics. It has the additional benefit of formalising the heuristic control algorithm of STAR, and providing a much more generalisable approach. The results indicate STOMP retains the performance and safety of STAR, spending approximately 87% of time in the 4.4-8.0 mmol/L BG band and 0.06% of time BG $< 2.2$ mmol/L, while considerably reducing clinical workload, requiring 35% fewer BG measurements. The GC performance and reduced workload of STOMP can be largely attributed to the 6-hour prediction horizon used, giving the controller better foresight into the interventions given. Overall, the STOMP protocol is a promising to development to the STAR protocol, enabling easy customization to a more diverse range of clinical practice cultures, cohort-specific approaches, and patient-specific conditions. However, a clinical pilot trial should be undertaken to confirm the results of this study.

Previous literature has highlighted the potential benefits for early basal insulin therapy as an preventative treatment for individuals with type 2 diabetes. In particular, in regard to preservation of endogenous insulin secretion and improved GC. However, limited literature exists around whether or not basal insulin therapy supports or suppresses endogenous insulin secretion. Therefore, a clinical

trial was designed which aims to gather data to investigate the affect of basal insulin therapy on endogenous insulin secretion, and develop a model to help us better understand and eventually safely, and effectively control the type 2 diabetes out-patient cohort. If the data from this trial shows basal insulin therapy to be a potentially viable preventative treatment for type 2 diabetes, it could provide a relatively safe and effective way of reducing/stopping the progression of type 2 diabetes.

An observational subcutaneous insulin trial was designed to investigate the idea of insulin being used as an initial treatment option for type 2 diabetic out-patients. The initial results and raw data analysis of the first two patients show no major concerns of patient discomfort and safety occurred. Issues around nurse workload were identified in the first trial patient, which resulted in the need for external research nurses in future patients. The measurement timing appears to capture the patient's meal response, peak and postprandial decay, well through out the day. Measurements were sometimes missed due to issues with blood draw from the peripheral IV line. This was a issue common to both patients and may have resulted in increased occurrence of haemolysis in the second patient, reducing the reliability of plasma insulin measurements. A solution to the complications with peripheral IV lines should be considered for future patients.

Overall, the research performed was designed to develop the STAR protocol and associated ICING model for GC of out-patients with pre-diabetes and type 2 diabetes. Interpolating sparse raw BG measurements with linear interpolation allows for better interpretation of intermediate BG dynamics, and thus identification of model-based $S_I$, with minutely or hourly resampling providing a fair assessment of GC performance statistics. The stochastic models used by STAR were shown capture patient $S_I$ variability well, while being generalizable across independent cohorts, and can be approximated with piece-wise polynomial functions. A physiologically more realistic representation of the ICING model's $S_I$ was created, improving the representation of BG measurements and associated error. The developed representation of $S_I$ can more optimally interpolate sparse, variable data and could be easily used with sparser out-patient data. STOMP, piece-wise polynomial stochastic models, and a minimal workload stepped feeding protocol provides a simpler and made

more clinically flexible alternative to the STAR GC protocol, while maintaining GC performance and safety. Ultimately, STAR is better validated and incrementally simplified for the out-patient setting. Finally, a clinical trial was designed and implemented to investigate basal insulin therapy for out-patients with pre-diabetes or type 2 diabetes, and develop our understanding of the metabolic characteristics of this cohort.

# Chapter 13

# Future Work

This thesis investigated many issues around the representation of $S_I$, GC provided by STAR, and understanding the type 2 diabetic out-patient. In many areas solutions were offered which improved the representation or outcome. However, in some areas a solution was unable to be offered, but areas of future improvement or development were revealed.

## 13.1 Stochastic model

The stochastic model was shown to represent the 1, 2, and 3, hourly changes in stepwise $S_I$ well. However, the path of $S_I$ to reach its final predicted $S_I$ value is not considered. Creating a stochastic model which provides a $5^{th}$ and $95^{th}$ percentile $S_I$ future path in time may allow for better forward prediction of a patient's BG dynamics. This type of stochastic model could be easily implemented into the current STOMP control framework. In addition, an investigation into where individual patient's lie within the stochastic model may allow for an adaptive stochastic model to be developed. One which dynamically changes it's stochastic bounds if patients lie within the same region as they become metabolically stable, and allowing for tighter GC to be provided.

Future work should also examine the maximum $S_I$ value which causes the STAR controller to offer the same treatment option regardless of state. This value should be used to define the upper bounds of the stochastic model used by STAR. Note, physiological limits cannot be used in this instance, due to $S_I$ being mathematically identified.

The creation of wide continuous B-spline basis functions poses an issue for real time identification of $S_I$. As the current $S_I$ value can change depending on the future BG measurements, the currently used stochastic model cannot be used. Instead, a method needs to be developed which considers a proportion of past $S_I$ values to predict the future $S_I$ value or path, minimising the impact of the current $S_I$ value changing. Additionally, creating a stochastic model which considers the past $S_I$ path and the most likely future $S_I$ path may again allow for better for prediction of a patient's BG dynamics.

## 13.2 Clinical GC

As the feeding of patients appeared to be major concern of clinical staff, a helpful addition to the STAR graphical user interface (GUI) may be a display of total calories and the percentage of caloric goal achieved from all sources, enteral and parenteral, over the last 12-24 hours. This would give the clinical staff a better indication of a patient's caloric requirements and what has been achieved, given clinical feed stoppages and gastric residuals. In addition, the STAR variable feed regime should be allowed to increase up to 120% goal feed to account for caloric losses during clinical feed stoppages, as currently implemented in STOMP.

A stepped feeding protocol by day showed promising results in virtual trials. However, a clinical trial comparing the variable and stepped feeding regime should be carried out to confirm the GC performance, safety and workload associated with this type of feeding regime. In addition, the clinical opinion of this type of feeding regime should be assessed to ensure effective clinical implementation.

STOMP was shown to provide very similar GC safety and performance in virtual trials, and potentially allowing 4 hour measurement intervals. A clinical trial evaluating the STOMP controller should be carried out to confirm the results of the virtual trial and determine if 4 hour measurement intervals can be offered. In addition, the cost functions used by STOMP should be integrated into the GUI of the tablet, visually showing clinician's the relative importance of each aspect considered in control.

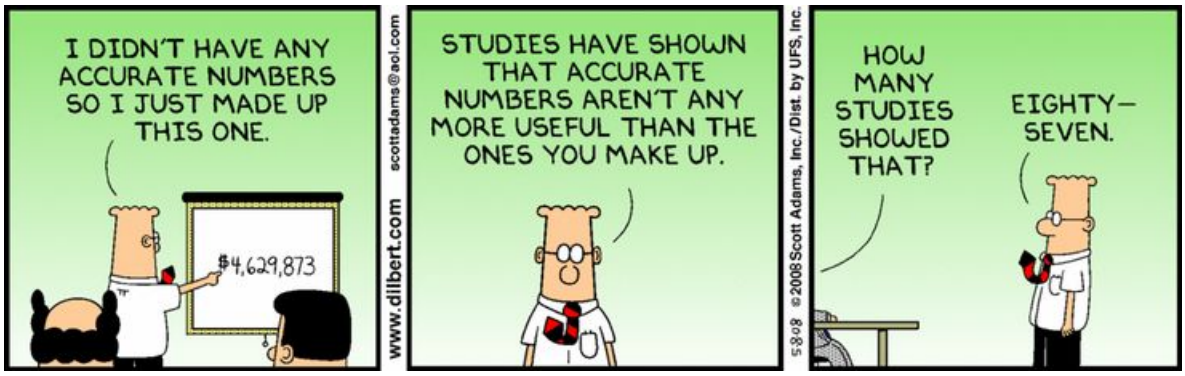
Another aspect that became apparent through consultation with clinical staff, was the lack of understanding of how STAR worked and why it is important to control BG levels. This may considerably contribute to compliance of STAR when first implemented in new units or used by new clinical staff, where *'trust'* of the protocol is still in development, as seen in Malaysia. A useful resource for current and future clinical implementations may be a series of short (approximately 2 minutes) and simple training videos explaining the concepts of STAR and GC in layman's terms. Subtitles would aid translation into any language. The ability for these videos to be accessed directly from the STAR tablet application will allow for very easy nurse training, and help improve clinical implementation to a foreign clinical practice.

## 13.3 Type 2 diabetes ward GC

The clinical trial currently under way should be continued until 10 patients have completely finished the trial. From the clinical data an effective insulin-glucose model should be able to be developed for this specific out-patient type 2 diabetic or pre-diabetic cohort. From my observations, there appears to be a difference of endogenous insulin secretion on and off insulin in the ICU cohort, therefore a robust model of endogenous insulin secretion off insulin should be developed for both the ICU and out-patient setting. Moreover, the ICU endogenous insulin secretion model should also consider the suppression of endogenous insulin secretion from exogenous insulin. From these models the question around basal insulin support for pre-diabetic individuals should be able to be answered.

From the trial data collected, a robust model of gut dynamics should be investigated. The influence of macro nutrients on glucose appearance dynamics should be validated and compared to that seen in the ICU. Ultimately, a predicted glucose response to a given meal should be developed to better equip GC protocols for dosing around previous and future meals.

If basal insulin support improves an individual's ability to control BG levels, a larger clinical trial should be undertaken which evaluates GC performance and safety of this treatment more robustly. In addition, a basal insulin dosing regime should be developed to be used in this trial, based on the results and model developed from the initial trial.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HOW MANY STUDIES SHOWED THAT?
EIGHTY-SEVEN.

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# Appendix

## Thesis Related Journal Publications:

**Chapter 5: K. W. Stewart**, C. G. Pretty, H. Tomlinson, F. L. Thomas, J. Homlok, S. N. Noémi, A. Illyés, G. M. Shaw, B. Benyó, and J. G. Chase, "Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis," Ann. Intensive Care, vol. 6, no. 1, p. 24, 2016.

**Chapter 7: Stewart KW**, Chase JG, Pretty CG, Shaw GM. Nutrition delivery of a model-based ICU glycaemic control system. Ann. Intensive Care. 2018;8:4.

**Chapter 9: K. W. Stewart**, C. G. Pretty, H. Tomlinson, L. Fisk, G. M. Shaw, and J. G. Chase, "Stochastic Model Predictive (STOMP) glycaemic control for the intensive care unit: Development and virtual trial validation," Biomed. Signal Process. Control, vol. 16, pp. 61–67, Feb. 2015.

### Currently in review:

**Chapter 4: Stewart, K. W.** , Pretty, C. G., Shaw, G. M. and Chase, J. G. (2017) 'Creating Smooth SI. B-spline Basis function representations of insulin sensitivity', Biomedical Signal Processing and Control.

**Chapter 8: Stewart, K. W.** , Chase, J. G., Pretty, C. G., and Shaw, G. M. (2017) 'Nutrition delivery, workload and performance in a model-based ICU glycaemic control system', Computer Methods and Programs in Biomedicine.

## Thesis Related Conference Publications:

**Chapter 2: K. Stewart**, F. Thomas, C. Pretty, G. Chase, and G. M. Shaw, "How Should We Interpret Retrospective Blood Glucose Measurements? Sampling and Interpolation," in 20th World Congress of the International Federation of Automatic Control, 2017.

**Chapter 3:** G. M. Shaw, **K. W. Stewart**, J. Dickson, C. Pretty, and J. G. Chase, "THE SECRET TO SAFE, EFFECTIVE AND SUCCESSFUL INSULIN DOSING," in 41st ANZICS/ACCM

INTENSIVE CARE ASM, 2016, p. 281.

**Chapter 3: K. W. Stewart**, J. Dickson, C. Pretty, G. Shaw, and J. G. Chase, "Variability is a constant! Insulin sensitivity and its variability in 4 ICU Cohorts.," in 16th Annual Diabetes Technology Meeting, 2016.

**Chapter 5: K. Stewart**, C. G. Pretty, F. Thomas, G. M. Shaw, T. Desaive, B. Benyo, J. Homlok, A. Illyes, N. S. Nemedi, and J. G. Chase, "Generalizability of a Nonlinear Model-based Glycemic Controller," in 4th IFAC International Conference on Intelligent Control and Automation Sciences (ICONS), 2016, vol. 49, no. 5, pp. 212–217.

**Chapter 6: K. W. Stewart**, J. Dickson, C. Pretty, F. Thomas, G. Shaw, and J. G. Chase, "High Compliance = Good Control? Compliance of the Stochastic TARgeted (STAR) Glycemic Control Protocol," in 15th Annual Diabetes Technology Meeting, 2015.

**Chapter 8: K. W. Stewart**, C. Pretty, J. G. Chase, and G. M. Shaw, "The Effect of Variable vs Fixed Feeding on Glycaemic Control in the Adult ICU: Virtual Trial Evaluation," in 20th World Congress The International Federation of Automatic Control, 2017.

**Chapter 8: K. W. Stewart**, J. G. Chase, J. Dickson, C. Pretty, and G. Shaw, "Can we fix it? Yes we can! Simplifying nutrition in STAR Glycemic Control.," in 16th Annual Diabetes Technology Meeting, 2016.

**Chapter 9: K. W. Stewart**, C. G. Pretty, H. Tomlinson, L. Fisk, G. M. Shaw, and J. G. Chase, "Stochastic Model Predictive Glycemic Control for the Intensive Care Unit: Development and virtual trial validation," in 14th Annual Diabetes Technology Meeting, 2014, pp. 342–485.

## Thesis Related Awards/Scholarships:

- Attendance of 9th HOPE, Meeting Nobel Laureates (1 in 5 from NZ) (2017)
- Claude McCarthy Travel Grant (2016)
- Marie Curie Fellow, Hungary collaboration (2015)
- UC Top Domestic PhD Student - Brownlie Scholarship (2014)
- Gold student research prize. Diabetes Technology Meeting, Bethesda, USA (2014)